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# POSTVACCINIAL PERIVENOUS ENCEPHALITIS

A PATHOLOGICAL ANATOMICAL STUDY ON THE PLACE OF POSTVACCINIAL PERIVENOUS ENCEPHALITIS IN THE GROUP ENCEPHALITIDES (THE DISEASE OF TURNBULL - LUCKSCH - BASTIAANSE)

*by*

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# PREFACE

The encephalitis that sometimes occurs following vaccination against smallpox has for some time been a subject of investigation in the Netherlands. After World War II, when it was possible for this research to be resumed, I was invited to take part in the investigations by the late Dr. F. S. Van Bouwdijk Bastiaanse, who had been a member of the Encephalitis Committee of the Netherlands Health Council since 1925. This invitation was a consequence of the institution of an Advisory Committee to the Health Organization T.N.O.—a branch of the Central Organization for Applied Scientific Research (T.N.O.) in the Netherlands—with the investigation of the causes of postvaccinial encephalitis as its object.

The support of this Organization, together with the opportunity to use the material in the Neuropathological Laboratory of the Utrecht University and the availability of the material previously collected in that laboratory, enabled me to carry out an investigation into the histopathology of postvaccinial encephalitis, the results of which are presented in this book.

Acknowledgements are due to the staff of the Neurological Clinic of the Utrecht University, especially to the Director, Prof. W. G. Sillevis Smitt, for their pleasant and helpful co-operation.

The discussions in the Health Organization T.N.O. have always been a stimulant to my work and I wish to express my gratitude to all who have taken part in the discussions.

I am also grateful to Mrs. J. L. A. M. Zwanikken for her assistance in reviewing the literature.

I should also like to thank Dr. Dorothy Russell for her help, her kind permission to use her laboratory enabled me to examine Dr. Turnbull's original slides on postvaccinial encephalitis, which are kept in the London Hospital.

Finally, I should like to pay tribute to the late Dr. F. S. Van Bouwdijk Bastiaanse, by whose moving spirit the entire investigation has been guided since the first reports on postvaccinial encephalitis appeared.

*Utrecht, September 1959*

ERNST DE VRIES

# CONTENTS

*Chapter 1*

# INTRODUCTION

Postvaccinial encephalitis still offers problems both as to its nosological place and its aetiology and prevention or therapy. It has been our aim in the present article to group together the facts that pathological examination of many cases which occurred in The Netherlands from 1925 up to the present time can offer, and to add some data from the literature pertinent to our problem.

The basic idea underlying the present investigation has been to bring together facts pointing to a separate nosological position of perivenous encephalitis in the group of para-infectious cerebral lesions and to avoid grouping them together with cases of a different pathology We therefore follow a principle opposed to the clinical method of grouping together, in the discussion of a disease, many borderline cases The clinical syndrome, with us, should come in the second place, and the borderline cases should be divided, according to their pathology, into cases belonging to the disease under discussion, or to other diseases or conditions.

The histological picture of perivenous encephalitis differs from the wellknown changes in inflammation of the nervous system due to viral infection. It should also be distinguished from the para-infectious vascular reaction types, and it is at the same time different from the experimentally produced allergic reactions of the brain, a special group of which it sometimes resembles

This work is an attempt, not to compare a clinical disease with a pathological picture, but *to see whether a monomorphous reaction of the C.N.S. is caused by as simple an aetiology as we can conceive* Therefore, clinical postvaccinial encephalitis need not necessarily show an uniform histopathology We want to stress this fact Sometimes

on following vaccination, many times following measles or other exanthematous diseases, a pathologically different reaction of the C.N.S. is seen (haemorrhagic, or encephalopathic), a point which is not mentioned by many authors. B. Walthard and K. M Walthard (1958), in their article on encephalitis following vaccination, variola, measles or varicella, give the impression that the only type of cerebral reaction following these diseases is perivenous encephalitis, they then must accept the encephalopathic changes, found as the only changes in many cases, as a fulminant reaction. They do not mention other reaction types. For us it is precisely the occurrence of these negative cases which, in the future, must give us a better understanding of the "gemeinsame Auslösemechanismen" (H. Jacob, 1958, p. 692) in diseases of the C.N.S. and the complicating factors which can alter the primary histopathological picture.

As a working hypothesis we accept for the present that perivenous microglial infiltration in a demyelinated area is caused by a specific factor, either endogenous, or exogenous in origin. *We accept that in biology as well as in physics the same cause, acting on the same tissue must have the same effect.* Van Bogaert (1950, p. 234) speaks of a standard form of reaction of the nervous tissue, determined by the tissue itself and independent of the causative agent. For us the character of this causative agent is as important as the endogenous constitution for the *occurrence of perivenous encephalitis. If the specific factor* were endogenous, it would mean a certain reaction type of the individual, as accepted by Scholz, H. Jacob and others. Probably this holds true in many cases when differences in heredity (van Bogaert, 1937; Sillevis Smitt, 1952) or constitution exist. These latter are acquired by the patient during life (allergic sensitization, preceding brain diseases, changes in the blood-brain barrier, etc.).

However, if the factor were exogenous, then the difference between perivenous encephalitis and other types would depend on a factor which might be a living agent or some kind of antigen or other toxic substance Perhaps we must not even think of a factor necessary to produce the perivenous type, but rather of the lack of a factor prohibiting this type of histopathological reaction to occur.

We wish again to stress the specificity of perivenous glial proliferation, because when for example haemorrhage occurs in postvaccinial encephalitis, this may be due not to the vaccination, but to another additional factor (*e.g.* bronchopneumonia or another infection) and is therefore not an essential part of the disease we are discussing (see Chapter 3, b. 4). Many authors do not differentiate between these pictures and then, when finding haemorrhages in one case of perivenous encephalitis, state that this belongs to the histological picture of this disease; a conception we do not wish to adopt.

I will use, in the following pages, the name *microglia encephalitis* to separate this particular type from other pathological changes. This is necessary because, in many articles on postvaccinial encephalitis, no differentiation is made between this microglial type and embolic encephalitis, and certain vascular encephalopathies. Formerly they have always been grouped together and in statistics and tables no distinction was made, which, in my opinion decreases their value. The name *perivenous encephalitis*, coined by Spatz for the same purpose, is now used by many authors for cases of postvaccinial encephalitis clinically diagnosed before an autopsy could prove this diagnosis—or disprove it. Radermecker (1937). a girl recovered after encephalitis following varicella, six days after the skin eruption, but she was exposed to the sun the day before. This case may as well have been insolation, and the name perivenous encephalitis should not be used This name is also often used in the literature for circulatory disturbances. Zulch (1954) describes his cases 9, 10 and 11 as typical perivenous encephalitis, although no microglial proliferation is mentioned and the description points to a vascular origin of these foci Moller (1949) uses the name perivenous encephalitis for many cases, including foci with central necrosis with a lymphocyte cuff (plate III, Fig E). It is for this reason that, in the subsequent study, *the name microglial encephalitis will be exclusively used for cases in which autopsy proved this perivenous microglial type of encephalitis to be present.*

A further restriction is necessary to differentiate microglia encephalitis from those cases of disseminated encephalomyelitis in which perivascular foci of demyelination and microglial proliferation occur,

but which show a marked reaction of the vessel walls, proliferation of histiocytes and plasma cells with often much larger lesions and fewer foci. The clinical course also differs; it may be subacute or recurrent. For these cases the name perivenous encephalitis is also often used (van Bogaert, 1950; Lhermitte, 1950) and, therefore, we prefer to use a special name for the material under discussion.

In examining the pathology of the Dutch cases of postvaccinial encephalitis, our attention was soon drawn to the fact that infants under two years never showed the wellknown histological picture (de Vries, 1955), but they did show other changes which ranged from embolic encephalitis to encephalopathy. It also became apparent that microglia encephalitis is a separate disease recognised as new in 1923, which follows only a few (exanthematous) diseases and shows a sharply defined clinical course. These facts enabled us to describe many cases in detail, thereby helping to elucidate the many still dubious points.

**Definitions**

Our purpose in giving definitions of a number of terms used in the following discussion, is not to choose between those already in use, but only to circumscribe in which sense words are used here.

*Inflammation*, as seen by the pathologist, is a complex reaction of an organ or part of it to damage caused by living or inanimate forces which can be present in various combinations and grades of action The name inflammation is of necessity more or less arbitrarily used, as a sharp distinction between inflammation and degeneration does not exist in biology

We can describe certain changes seen in an organ as an inflammatory reaction, but whether we shall call the disease which causes these changes an inflammation depends not only on the distribution of the inflammatory changes, but also on the occurrence of other changes which could be more important in the general picture of the disease (*e.g.* degenerative diseases often show inflammatory lesions in some parts). When we accept, in accordance with the general pathology, as necessary changes constituting an inflammatory reaction,

proliferation, alteration and exudation, we again have difficulty when one of these factors is predominant, and another nearly absent. All grades occur in our histological pictures, but we have only few names to describe them. Thus encephalitis and encephalopathy do not have a sharp borderline and one author will group with the encephalitides cases that another author calls encephalopathies (see Radermecker's discussion of this point, 1958). We therefore feel that, in the following pages, we should try to define sharply the inflammatory reaction as seen in the tissues from other reactions, but that a separation of an inflammation from a degeneration as type of disease will necessarily be vague. Globus differentiated between inflammation and inflammatory reaction years ago; it is also accepted by Jacob (1956).

It will in the future be necessary to search for the rôle of the elementary processes acting together in an "inflammation", to judge of the value of this word in a given case. A difficulty arises in neuropathology, as one of the most typical elements of the inflammatory changes, *viz.* the polymorphonuclear leucocytes, function and behaviour of which in the tissues are rather well known, play only a minor rôle in the encephalitides which interest us now. About the function of the mononuclear small lymphocytes, however, very little is said in general pathology. This explains that we do not know whether the absence or presence of small lymphocytes in the tissues is important in grouping a certain picture with the inflammations or not. If Ehrich (1957) is right that the lymphocytes play a rôle only in the reparative stage of tissue reaction, then they ought not to be regarded as a sign of inflammation. Link and Schleussing (1958) attribute an antitoxic reaction to the lymphocytes and think that they have some function in the assimilation and dissimulation of fatty products.

Another difficulty in neuropathology is the rôle played by the microglia and other glial cells. Is hyperplasia of glia cells equivalent to the proliferation of mesenchymal cells in other organs? We will not discuss this point, but have mentioned it to demonstrate the difficulties that may arise when we try to give precise definitions

Continuing our discussion of the pathological side of our problem the name *encephalitis* will be used here to designate various types of

reaction of the nervous tissue to damage, either by living agents or chemical substances. It is thought inopportune to give a very precise definition, as this must necessarily differ from definitions used by other authors and might cause more misunderstanding than it would clarify the subject. *This implies that no sharp differentiation will be* made between encephalitis and encephalopathy. Also, in certain cases, a division into degeneration and inflammatory lesions will be difficult, and many histological pictures can be interpreted either as a degeneration or as an inflammation.

In general we shall use the word *encephalopathy* when vascular changes, other than cellular exudation dominate the picture (but *including haemorrhages*), and *degeneration when changes in nerve* cells or nerve fibres prevail. But sometimes encephalitis may cover both these extremes of reaction to damage.

Spielmeyer differentiated between primary and secondary inflammation, *thereby* introducing an *aetiological factor in the histological* definition. This is quite logical but very difficult to handle in any particular case with obscure aetiology. These words are cumbersome and will never come into general use. It is for this reason also that we cannot follow Ferraro, when he proposes to divide his material into cases of leucoencephalitis, when an infection is the cause; leucoencephalopathy, when caused by intoxication, and leucodystrophy, when degeneration is the cause. In many cases we cannot wait with a classification or denomination until the final word is said about the pathogenesis and aetiology and then, naturally, mistakes have already been made which it will be difficult to correct afterwards. We therefore prefer to use the names either without a sharp definition or by adding adjectives that will give them a certain meaning The tendency to use the word inflammation only for reactions to a living agent, is very widespread (Radermecker, 1956, p. 3), but most authors do not follow this use systematically because it is in contradiction with the original conception.

The word microglial encephalitis, as pointed out, will be used only for cases in which *autopsy shows perivenous* demyelination with microglial proliferation in the demyelinated areas, without or with

only slight changes in the vessel wall, and together with other signs which will be described in detail in Chapter 3. Here, a great number of foci are present in the cerebral hemispheres, prevailing in the white matter. The word is therefore not used for the cases generally known as disseminated encephalomyelitis, with larger lesions, more tissue destruction and a different clinical course, nor for cases showing only the perivenous foci without the other characteristics, but sometimes together with other changes.

*Postvaccinial encephalitis** comprises the cases, clinically following smallpox vaccination within about 4 weeks, showing a clinical picture of encephalitis. This group will therefore consist of cases of microglia encephalitis and other diseases. When a Heine-Medin infection is activated by vaccination and encephalomyelitis follows, this also is postvaccinial encephalitis and, as perhaps constituting a risk of vaccination, worth to be included in our investigations.

The *clinical aspect* of the use of the name encephalitis has to be commented on. The clinician regards encephalitis as a disease of a patient, and not as a reaction of a part or of one organ[1] Therefore there can be no absolute parallelism between the clinical diagnosis of encephalitis and the histological picture of changes in the C.N.S. However, the inflammatory reaction in any part of the brain, found at autopsy, should direct the final diagnosis of encephalitis, when the changes are assumed to be primary and to constitute the most important part of the findings But when exudation and degeneration are secondary (*viz.* in fat embolism, salvarsan brain purpura, etc.) the name encephalitis should preferably not be used.

The distinction of clinical encephalitis as a syndrome, from pathological encephalitis as a local histological change, is also made by Scholz and by Lhermitte (1950), and others When a patient shows fever, general brain symptoms, malaise (functio laesa), and when autopsy reveals oedema and hyperaemia of the brain, the diagnosis encephalitis seems clinically justified, although histological examination may only show encephalopathic changes.

* Postvacc*inal* when following smallpox vaccination, postvacc*inal* when following vaccinations in general, is the logical orthography, it will be generally used here

The literature on postvaccinial encephalitis gives numerous examples of cases clinically diagnosed as such but, at autopsy, showing pictures varying from pneumococcus sepsis to poliomyelitis or normal brains (Gins, 1931, and others). Many authors still group most of these pathological changes together as the pathology of one disease, in which we shall not follow them. When Comby (1935) states that all postvaccinial encephalitides in infancy constitute an indivisible group both clinically and aetiologically, science cannot profit by her documentation and discussion It is on the contrary the aim of the present study to try to delineate smaller disease units by dividing the large clinical group of post-exanthematous encephalitides into smaller units, each consisting of cases similar or identical in their pathology, clinical course, pathogenesis, and perhaps aetiology.

We follow here the method of H. Jacob (1954), who isolated from the large group of post-infectious encephalitides the diffuse lymphocytic encephalitis as a type with hitherto not fully known aetiology, but ultimately probably due to a certain combination of factors

Postvaccinial encephalitis is classified by various authors in different ways. Some, using the name para- or post-infectious disease, group it together with the changes following infections, intoxications and general disease (Scholz, 1957; Kinnier Wilson, 1940; Biemond, 1946). Pette (1942) groups it together with disseminated encephalomyelitis, multiple sclerosis and some forms of diffuse sclerosis under the heading. demyelinating forms of non-bacterial encephalitis. Verlinde (1947) groups perivenous encephalitis following measles, varicella and smallpox vaccination as one type of leucoencephalitides, whereas Globus (1932) and Hassin (1948) put it down as a separate unit in their system of encephalitides.

## Classification

A classification based mainly on the pathological changes was suggested by Spatz (1931) and later slightly modified by Hallervorden (1943) and van Bogaert (1950). A summary is given here.

1. Meningo-encephalitis (tuberculous, purulent, etc.)

2. Metastatic, embolic encephalitis with multiple perivascular foci (in endocarditis, sepsis, etc.)
3. Polio-encephalitis, diffuse, mainly telencephalic (dementia paralytica, pan-encephalitis of Dawson-van Bogaert, etc., or the acute form of Pette-Doring)
4. Polio-encephalitis, mainly focal distribution (epidemic encephalitis, Heine-Medin infection; some authors include rabies)
5. Focal demyelinating encephalitis (multiple sclerosis; some forms of diffuse sclerosis; acute encephalomyelitis disseminata and neuropticomyelitis)
6. Multiple focal perivenous encephalitis (postvaccinial; postmorbillar; postvaricellar and some cases following other affections)
7. Polio-encephalitis with glial nodules (typhus is a typical example; encephalitis japonica; St. Louis encephalitis; Russian spring-summer encephalitis probably also belong in this group; perhaps some cases of Pette-Doring's pan-encephalitis)
8. Diffuse encephalitis (African trypanosomiasis). Does dementia paralytica belong here or under 3?
9. As yet unclassified cases.

I will add for the sake of convenience, and as seen from a clinical standpoint

10. Encephalopathies, with hyperaemia, oedema, haemorrhages, degeneration, oligodendroglial reaction, reticulo-endothelial proliferation, *i.e.* the so-called haemodynamic syndrome of van Bogaert (1947).

Link and Schleussing (in Handbuch der Spez. Pathol Anat Bd XIII, 2, p 205, 1958) regard para-infectious encephalomyelitis of varying origin as a separate group of leuco-encephalomyelitis.

This brief enumeration sufficiently shows that no classification satisfactory to the clinician, the pathologist and the epidemiologist has hitherto been made Whether this will be possible when the aetiology of these diseases is understood, remains to be seen

For nosological purposes the word *diffuse* had better be discarded, as it is used sometimes meaning *multiple* (as in perivenous encephalitis

following vaccination, which consists of rather sharply demarcated lesions, with normal parenchyma between the foci). Otherwise the term *diffuse* must be reserved exclusively for changes such as seen in dementia paralytica.

The names leuco- and polio-encephalitis do not imply an absolutely sharp localization in either of these structures; generally this distinction is only valid in the cerebral and cerebellar hemispheres, and it is then of a certain value for classification In the deeper structures, leuco-encephalitis of vaccinial origin is also widely present in the grey nuclei, as also in other diseases included in this group. Again, in poliomyelitis of the Heine-Medin type, lesions in the white matter of the spinal cord and medulla oblongata are rather common.

Our aim in the future must be to determine the pathological changes that are specifically found with a certain aetiology, not only in post-infectious disease in general but also those connected with the more elementary aetiological factors. These can obtain in the individual, *e.g.* a certain degree of specific immunity to the infection; allergic disposition; acute or subacute reaction; general weakness; sensitization of the brain due to previous trauma or disease; coincidence with other vaccinations or serum injections or diseases which often show nervous complications (*e.g.* whooping cough), etc. On the other hand, differences in the virus may be important: neurotropic strains; dose of virus at the side of invasion; portal of entry and perhaps mutants, with some specific characteristics. The medium in which the virus is transported may also play a certain rôle.

This brings us to a consideration of the value of slight *deviations from the normal type.* In a few cases of postvaccinial encephalitis, topical loss of groups of large ganglion cells is found; in others, the incubation period is much shorter or longer than is usual; large lymphocyte cuffs may be present, etc. In these cases we should not confine ourselves to saying that the case is atypical, or that there are complications, but we must look for the additional factors in the aetiology or pathogenesis, as discussed above.

The course of the disease may be altered by high fever, by con-

vulsions with focal destruction of nervous tissue or by marked hyperaemia with small haemorrhages or with oedema of the brain. The changes found at autopsy in these cases should not all be ascribed to the primary disease!

We believe that when all these things will be known, we shall no longer say that any kind of infection in the brain can cause any type of reaction, but that a certain combination of aetiological factors always induces the same specific reactions

*Chapter 2*

# MATERIAL

The present article mainly deals with autopsy cases of postvaccinial encephalitis that occurred in the Netherlands after 1925. With the exception of cases 1, 2, 4 and 6, all were examined by the author, and of those 4 cases satisfactory descriptions were available. Fatal cases without autopsy and those of which no slides were available for study were excluded from the present study. The material therefore *does not lend itself to statistical elaboration*

Only cases with an incubation period of 21 days or less are considered, as it is generally accepted that perivenous postvaccinial encephalitis does not start beyond that period. Nervous diseases *starting more than 3 weeks after vaccination, are either due to* complications (purulent processes, etc.) *or* are independent of the vaccination. Perivenous encephalitis has not been found in cases with an incubation period exceeding three weeks (see, however, Chapter V c, case de Busscher and Radermecker). A complete list of our cases is given in Table I (p. 13)

The frequency of cases during the 34 years covered by this survey was unevenly distributed, this was partly due to external circumstances very few vaccinations were performed after compulsory vaccination was stopped in 1930 Then the age of primary vaccination was lowered from about 5 years to the first or second year of life.

In recent years, from 1952 onwards, more attention has been paid to cases of cerebral damage following vaccination which were clinically atypical, either with a very short incubation period, or with a different clinical picture. This explains why many cases of this period showed a pathology other than perivenous encephalitis.

In addition, human material of other types of encephalitis could

TABLE I

DUTCH AUTOPSY CASES OF POSTVACCINIAL COMPLICATIONS USED IN THIS ARTICLE
P = Primary vaccination. R = Revaccin. V = vaccinia generalisata
+ = Microglia enc. — = Other pathology.

| *Case No* | *Year* | *Age* | *Incubation days* | *Vaccin.* | *Death following vaccin. days* | *Microglia encephalitis* |
|---|---|---|---|---|---|---|
| 1 | 1925 | 3 y. | 11 | P | 17 | + |
| 2 | | 5 y. | 12 | P | 16 | + |
| 3 | 1926 | 5 y. | 10 | P | 20 | + |
| 4 | | 4 y | 11 | P | 16 | + |
| 5 | 1927 | 3 y. | 12 | P | 19 | + |
| 6 | | 5 y | 12 | P | 21 | + |
| 7 | 1928 | 3 y. | 13 | P | 19 | + |
| 8 | | 4 y. | 11 | P | 14 | + |
| 9 | 1929 | 3 y. | 10 | P | 11 | + |
| 10 | | 5 y | 11 | P | 14 | + |
| 11 | | 7 y | 14 | P | 25 | + |
| 12 | | 13 y | 9 | R | 14 | + |
| 13 | | 13 y | 13 | R | 15 | |
| 14 | | 13 y. | 6 | R | 9 | |
| 15 | | 29 y. | 7 | R | 16 | |
| 16 | 1930 | 4 y | 12 | P | 18 | + |
| 17 | | 4 y | 10 | P | 17 | + |
| 18 | | 62 y | 11 | R | 15 | |
| 19 | 1940 | 10 y | 11 | P | 13 | + |
| 20 | | 6 mo. | 2 | P | 3 | |
| 21 | | 7 mo | 20 | P | 8 | |
| 22 | | 8 mo. | 5 | P | 6 | |
| 23 | | 9 mo | 14 | P | 21 | |
| 24 | | 10 mo | | V | 8 | |
| 25 | 1941 | 8 y | 11 | P | 12 | + |
| 26 | | 10 mo | 6 | P | 7 | |
| 27 | 1942 | 6 y | 11 | P | 16 | + |
| 28 | 1944 | 13 mo | 12 | | | |
| 29 | 1946 | 9 mo | 9 | P | 10 | — |

| Case No. | Year | Age | Incubation days | Vaccin. | Death following vaccin. days | Microglia encephalitis |
|---|---|---|---|---|---|---|
| 30 | 1947 | 3 y. | 13 | P | 21 | + |
| 31 | | 8 y. | 12 | P | 15 | + |
| 32 | | 9 y. | 14 | P | 22 | + |
| 33 | | 10 y. | 12 | P | 20 | + |
| 34 | | 8 mo | 5 | P | 9 | — |
| 35 | | 5 y | 5 | P | 6 | — |
| 36 | 1948 | 9 mo | 3 | P | 8 | — |
| 37 | 1951 | 19 y. | 12 | R | 19 | + |
| 38 | | 20 y. | 12 | P | 15 | + |
| 39 | | 20 y. | 13 | P | 15 | + |
| 40 | | 21 y. | 9 | P | 14 | + |
| 41 | | 22 y. | 13 | P | 19 | + |
| 42 | | 26 y. | 6 | R | 8 | — |
| 43 | | 56 y | 8 | R | 9 | — |
| 44 | | 68 y. | 17 | R | 24 | + |
| 45 | 1952 | 20 y. | 12 | P | 16 | + |
| 46 | | 8 mo. | 8 | P | ∞ | — |
| 47 | | 11 mo. | 8 | P | 9 | — |
| 48 | | 16 mo. | 10 | P | 11 | — |
| 49 | 1954 | 7 mo. | 7 | P | 7 | — |
| 50 | | 9 mo | 2 | P | $2\frac{1}{2}$ | — |
| 51 | 1955 | 9 mo. | 8 | P | 8 | — |
| 52 | | 24 mo. | 10 | | ∞ | — |
| 53 | 1957 | 20 y. | 13 | P | 20 | + |
| 54 | | 7 mo. | 9 | P | 10 | — |
| 55 | | 20 y. | 10 | P | 10 | — |
| 56 | | 21 y | 7 | R | 7 | — |
| 57 | | 11 mo | 24 | P | 24 | — |
| 58 | | 4 mo | 0 | P | 13 | — |
| 59 | | 14 mo. | 5 | P | 5 | — |
| 60 | 1958 | 17 mo | 18 | P | 18 | — |
| 61 | 1955 | 7 mo | 12 | P | 12 | — |
| 62 | 1958 | 6 mo | 5 | P | 5 | — |

be used for comparison, as also a number of animal brains with various spontaneous encephalitides, viral, bacterial or granulomatous. The experimental material consisted of some experiments, dating from earlier research into the aetiology of postvaccinial encephalitis, and some recent experiments Very little material of experimental allergic encephalitis was available for study.

A considerable part of the extensive literature has been read, especially to search for abnormal pictures. But we are aware that many important articles may have escaped our attention.

*Chapter 3*

# POSTVACCINIAL MICROGLIA ENCEPHALITIS

## a. General

In the introduction it has been mentioned that the name microglia encephalitis will be used for those cases in which autopsy revealed the perivenous type of demyelination and microglial proliferation, excluding abortive cases and the fulminant cases of encephalitis in *which only encephalopathic changes in the C.N.S.* are found after death. Some of these cases, however, are grouped by their authors with the perivenous type (see Chapter 6, a).

It is evident that only by narrowing down our concept in this way we can try to bring facts together for a final evaluation of the place of microglia encephalitis in the nosological system.

It is not the purpose of the present article to give a complete description of the pathology of postvaccinial encephalitis. This has been repeatedly done by many competent authors. The principal aim of this article, however, is to discuss a number of details as found in the great majority of the Dutch cases, which have come to autopsy and which could personally be examined by us.

In Table XIV (end of book) we listed the main facts of microglia encephalitis requiring discussion. As demyelination is present in all, it has not been listed. One purpose of this table is to follow up differences in the histological picture in cases of short and long duration. The cases are therefore arranged according to survival time after vaccination. The duration of actual nervous illness is given in Fig. 18 (p. 135), which shows that there is no correlation between the duration of incubation and that of the actual nervous disease.

The typical pathological changes of micr[illegible]li[illegible] encephalitis are the

following:

*General hyperaemia* of the meninges and parenchyma

| | *present* | *doubtful* | *absent* |
|---|---|---|---|
| in the meninges | 16 | 4 | 3 (Nos. 7, 27, 33) |
| in the parenchyma | 21 | 1 | 1 (No 17) |

It is remarkable that this symptom of inflammation was equally found in the cases of early death and those of late death, and was even still present in case 5, in which the nervous sypmtoms and histological examination had shown that the patient was on his way to recovery before a complication set in. It was sometimes thought that the congestion of the central veins of the foci was more marked in cases of more prolonged illness.

*Oedema and swelling of the brain.* General oedema of the brain was seen in 2 cases (Nos. 41, 53) and a slight cerebellar conus without broadening of the convolutions was found once (No 45) The brain weight may be found increased (No. 53). In this case the medulla oblongata was very much enlarged and this oedema and the widespread encephalitic foci in this region were the main cause of death in this patient (see history of this case in paragraph b 4).

Perivascular oedema was also found sometimes, although seldom, in the encephalitic foci.

*Meningeal cellular infiltration* was present in 24 out of 25 cases The intensity of this infiltration varied with different localizations, without any recognizable rule. The cells were small and large lymphocytes, and sometimes plasma cells were observed. Polymorphonuclear leucocytes occurred in three cases (Nos. 19, 39, 11), but only in two (Nos. 19, 11) in larger numbers. In these patients many congested blood vessels were found, filled with polynuclear cells, this evidently represented an early stage of a pyaemic condition or of purulent meningitis to account for the abnormal picture One of these patients had purulent cystitis.

Cellular infiltration of nerve roots, as described by Turnbull and by Perdrau, or of the spinal ganglia (Perdrau, Pette), was not seen in our cases

Case 39, mentioned above because of the number of polynuclears in the meninges, was somewhat different from the general picture; in some places the meninges contained many plasma cells and large lymphocytes, and a dense infiltration with glial cells existed in the underlying molecular layer of the cortex Perivascular microglial foci could also be found in all cortical layers at these same places. Observed with low magnification, the picture resembled purulent meningo-encephalitis, but the cell type was quite different and the ganglion cells remained normal in the foci (Fig. 1).

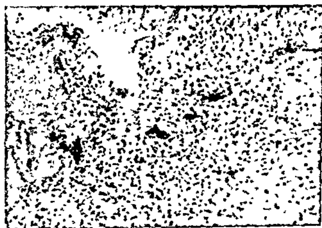


Fig. 1. Complicating purulent meningitis Case 39 Inflammation of meninges, invading the cortex and spreading along vessels

***b. Perivascular focal lesions***

*1. Foci*

The *distribution* of the foci along the cerebral axis differs from case to case. In the cerebral hemispheres foci prevail in the white matter, often abounding in one lobe (occipital more often than other lobes), and are in most cases also found in the 5th and 6th cortical layers In the upper layers foci are rare and small, sometimes resembling glial

stars In the cerebellum a cortical localization of the foci is extremely rare, and the name leucoencephalitis therefore seems justified. But in all deeper structures as well as in the spinal cord, a predilection for the white matter is less marked F. Lhermitte (1950) points out that the density of myelinated fibres in the grey substance is probably the most important factor. In the white substance, however, the compact parts (corpus callosum, internal capsule, pyramids) are generally much less involved than the more loosely built structures.

Finley (1950) thinks that the diameter and perhaps the function of the affected veins is the most important factor. According to him, the upper cortical layers do not show foci because they have only small veins, whereas the caudate nucleus, with a similar paucity of myelinated fibres, often contains foci around the large veins

In one case examined in reference to this point (No. 53), however, the very rare foci in the caudate nucleus were lying in or adjacent to fibre tracts, perforating this grey mass.

In a number of cases (*e.g.* our case 11) the spinal cord is seriously affected, whereas foci in the brain are scanty. This is especially marked in cases with the clinical picture of transverse myelitis, in most of which only few foci are found in the higher centres (see b. 5). The opposite condition may also occur. The foci in the subcortical white matter of the hemispheres are found along the veins running towards the ventricle, *i.e.* the places where we also find the lipochrome pigment from ganglion cell degeneration remaining for a long time. Other places of predilection are the larger veins, running dorsally from the olives, and those dorsally from the anterior horns of the spinal cord, and the median and paramedian veins in the posterior column The subependymal veins of the lateral ventricles are also often the site of larger foci.

Sometimes the localization in stem and cord is more or less symmetrical, but in other cases only one half of the medulla is affected (case 37), or we find one olive heavily affected, and the other quite free (case 3). The distribution of the foci is very irregular, a cross section of the cord or brain stem, or even of the subcortical white matter, often shows a number of foci lying rather close together

whereas adjacent parts may be free or much less involved. As will be discussed later (case 38), this area sometimes seems to be a place of increased vulnerability, due to an older lesion.

The total number of foci is generally very large. Their localization, especially when grouped together in larger numbers, is of course important as this may cause neurological symptoms.

As Lhermitte (1950) points out, the localization in the deeper parts of the brain stem, in pons and medulla is often responsible for a fatal development, the oedema being perhaps even more dangerous than the microglial proliferation.

When many foci are grouped in a small area there is a tendency to coalesce; but generally we can still distinguish the individual foci by which they differ from the larger foci of disseminated encephalomyelitis

*Demyelination* was present in all our cases and we did not find a conclusive difference in this respect between cases of longer and those of shorter duration. Our slides did not give any clear indication for a solution of the problem whether the microglial proliferation preceded the demyelination or was a reaction to it. Sometimes, however, the picture suggested that the cellular infiltration had been present before myelin changes became evident with our staining technique. *But it is very well possible that the microglia is more sensitive to the earliest chemical changes of myelin degeneration than our staining methods are.* This question is known to have arisen even in the earliest descriptions of postvaccinial encephalitis, and both views have had fervent advocates. In fatal cases, however, the histological picture is generally already complete; *an answer to the question could be found in cases of very early death,* or in cases of longer standing with development of new foci during the period of illness The occurrence of these new foci is denied by some authors, but we think there is evidence that this process actually takes place.

Roizin and Kolb (1957) approached this problem from the histochemical side and reached the conclusion that there is some evidence of abnormal enzyme reaction to the lipid material before this can be detected by the usual histological techniques

In our case 5, in which the encephalitis tended to healing, the lesions were rather small and the surrounding normal fibres came closer together. It may well be that no marked demyelination is visible after complete healing

The breakdown products of myelin degeneration were never very conspicuous. The foci never resembled a malacic lesion, with drops of myelin scattered everywhere. Generally, Sudan-stainable fatty substances were very scarce in the foci or their immediate surroundings but could be found in the sheaths of vessels at some distance, absorbed by granule cells. P.A S.-stainable material was only present in the foci in very fine granules or drops. We therefore believe that the glia cells dissolve the larger part of the degenerating myelin by some chemical reaction, which cannot be traced with our staining technique.

M. B. Schmidt (1944) explains this as adsorption of the fat onto proteins, which yields a soluble product.

In the earliest stages the microglia cells did not contain vacuoles which, however, became evident in later stages (see below). It is therefore certain that the main catabolism of the myelin substance is primarily effected by the microglia cells. Subsequently, oligoglia and astroglia probably take part in this process.

Little need be said about the *axis cylinders*. We found, as previously described by many authors, in some foci, all or nearly all axis cylinders intact, but a certain loss was as a rule visible, especially in larger foci

The microglia cells are lying free in the parenchyma around the vessels, sometimes their nuclei are elongated and very irregular, and the plasma is also elongated, with many processes. Other cells are shorter and may show more rounded nuclei. The latter type is more frequently seen with the cells lying close to the vessels. As a rule, the cells lying free in the periphery of foci have smaller protoplasmic bodies than the more centrally located cells, but they may also show vacuolation of their plasma (Fig. 2).

The origin of the microglia cells could not be determined with certainty, they are probably formed by amitotic division of the pre-existing cells I have never found conclusive pictures suggesting that multipotent vessel wall cells, infiltrating the tissue from the

vessels, develop into microglia cells, as C. de Lange states (1943). On the contrary, in many smaller foci with microglia cells scattered diffusely in the parenchyma, the vascular walls showed no hyper-



FIG 2 Microglia cells in a focus, showing vacuolisation of the protoplasm (X) Case 45, Nissl stain

trophy, and no cellular infiltration of the Virchow Robin spaces existed

Microglial cuffs existed in all our cases, and generally they were found at all levels of the nervous axis The total number of foci was practically the same in cases of death shortly after vaccination and cases of longer duration. This indicates that the foci develop at about the same time and that we can expect to find foci of different ages only in cases of short survival.

Fatty granule cells were present in 11 cases, doubtful in 2 and

absent in 8 cases. The earliest appearance was in case 10· 14 days after vaccination In the later stages their occurrence was constant and their number increased. These cells were most easily recognized by the vacuolated protoplasma in Nissl stains; often the Sudan reaction failed to give clear pictures. We gained the impression that the microglia cells in the periphery of a focus could show vacuolation of the protoplasm while still having the shape of rod cells (Fig. 2). Nearer the central vessel, the plasma processes became shorter and the nucleus tended to a spherical shape. An accumulation of round granule cells in the vessel sheaths, as found in malacic foci, was very rare. In some cases the fat stain showed that no fat was present in the focus but that the vessel sheaths at some distance contained granule cells laden with fatty substances

All granule cells originated from glia cells, there was no evidence that the mesodermal tissue also took part in their formation. Myelin lumps, as found in malacic foci and in fat embolism, were not present in our cases, evidently the myelin degeneration took place along another line of disintegration than in those diseases.

No definite explanation of this can be offered. It might be possible that from the start the microglia cells were more active in changing the myelin into soluble substances, or that myelin degeneration was more gradual But it is also possible (even probable) that other enzymes are active here, and give another catabolic product than in malacia

As already stated, material stainable with the P.A S method for polysaccharides was present in the foci only in very small drops, and was also rare along the vessels. However, pink staining patches of 5—15 μ were present in many fibre tracts, independent of the focal lesions It is not certain whether this must be considered pathological.

*Lymphocytes* The small lymphocytes must be discussed in some detail because uncertainty about their function still exists We group here the cells with a small, round and darkly staining nucleus and very scanty protoplasm. In the dense cellular aggregates around vessels, it is always difficult to determine the size of the protoplasm and several cells included by us in the lymphocyte group may have been micro-

glia cells in a stage before the nucleus enlarged, but after it had resumed the spherical shape.

In the table we have listed separately the lymphocyte cuffs around vessels without microglial proliferation (giving a picture as regularly found in common virus encephalitides) and the microglial foci, with lymphocytes and without them. It is quite evident that simple lymphocyte cuffs were very rare in our cases. In case 9 the child was affected by whooping cough before vaccination took place; in case 37 typhoid and cholera vaccinations were given during the incubation period, and case 11 suffered from purulent cystitis several days before death. This suggests that the occurrence of lymphocytic infiltration is due to, or at least increased by complicating toxi-infectious conditions. Lymphocytes mixed with microglia in the foci occurred fairly regularly, but in several of these cases bronchopneumonia was the cause of death, or septicaemic conditions existed

Comparing the number of foci without lymphocytes with the foci in which these cells were present, we gained the impression that the *small lymphocytes are not an essential part in microglia encephalitis.* They are not more numerous in the later stages than in the earliest stages, or the reverse, as stated by B. and K. M. Walthard (1958, p. 789). Large lymphocytes and plasma cells were sometimes noticed; this does not require special discussion.

*Polymorphonuclear leucocytes* were rarely found in the foci. It was sometimes difficult to distinguish the very irregular nuclei of microglia cells from polynuclears but generally the latter cells have smaller nuclei. The round and well-defined protoplasma of the polynuclears, however, can easily be recognized in Nissl-stained sections When only haematoxylin-eosin sections are available, however, distiction may be very difficult. I believe that many statements confirming the presence of polymorphonuclears in foci of microglia encephalitis are due to this difficulty (*e.g.* Wiersma). We found them only once in our material; more often, however, in the meninges (3 times), but always in small numbers

The *central vessel* is generally a vein of rather large diameter, and the impression is gained that the larger foci are lying around the larger

veins. Microglial proliferation is seldom found around an artery (case 3) and there is never a capillary as the centre around which microglia is arranged. We find, on the contrary, normal capillaries and smaller veins running through a focus without evident connection with it. The central vessel is generally filled with normal blood and the vascular wall shows no important changes However, in later stages or when destruction of the parenchyma is marked, some proliferation of the vessel wall can be found. This was also the case in No. 37, in which revaccination was given at the same time as injections against typhoid and cholera.

## 2. *Earliest stages*

In the literature it is generally accepted (van Bogaert, Scholz, Lhermitte, Radermecker) that perivenous encephalitis develops after an initial period of less obvious lesions of a more encephalopathic character. We do not think that the findings in our cases point in this direction.

Since death from perivenous encephalitis generally occurs on or after the 13th day following vaccination (see Fig. 3), these very early cases were regarded by the authors as running a *fulminant course*. When discussing this question, we have to separate the cases in young children (under 2 years of age) from the older group, because in these young children perivenous encephalitis has never been observed and it would be illogical to surmise that only fulminant cases occur, with a pathology differing from the picture in more prolonged cases. The cases in young children therefore belong to a special group, which will be fully discussed in Chapter IV b, on children under 2 years of age. This also pertains to the case of Rohmer, Sacrez, Rohmer (1947), cited by Lhermitte.

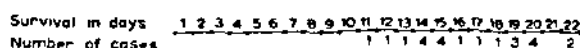



FIG 3 Survival time after vaccination in the Dutch cases of microglia encephalitis

The literature contains reports on 2 cases in older patients, described as fulminant cases of perivenous encephalitis, *viz*: a case by de Lange (1948) and a case by Doring (1942). A case described by Wigand (1941), following the eruption of rubella exanthema, is also regarded by the author as a very early case of perivenous encephalitis. Many other cases have been described in which histopathological examination only showed encephalopathic changes; these were not considered early stages of perivenous encephalitis, but regarded as another reaction in postvaccinial encephalitis

Complete understanding of the nosological place of these so-called fulminant cases can only be attained by comparing them with the earliest cases of well-developed microglial encephalitis. We will give the data on the 3 abovementioned cases, and compare them with 2 Dutch cases and the case described by Kokken (1937) (Table II). Hassin and Geiger's patient also died on the 13th day after an illness of 31 hours, showing the typical microglial picture

TABLE II

DATA OF SO-CALLED FULMINANT CASES AND OF EARLY MICROGLIA ENCEPHALITIS

| | *Case* | *Age in years* | *Incubation* | *Death in days after vaccin* |
|---|---|---|---|---|
| | de Lange | 5 | 6 | 6 |
| Encephalopathy | Doring | 27 | 13 | 13 |
| | Wigand | 10 | | 3 after eruption exanthema |
| | No 9 | 3½ | 10 | 11 |
| *Perivenous Enc* | No. 19 | 10 | 11 | 13 |
| | Kokken | 10 | 11 | 13 |

Death from microglia encephalitis in the Dutch cases occurred on the 11th to the 22nd day (Fig 3).

*Case C. de Lange*, 1948 Girl, born 13 11 41 *Mother suffered from rubella during pregnancy* In the family cases of Buerger's disease occurred The

child was healthy; vaccinated (primary) on 20.5.47. On May 26th she was noted to be drowsy, then had a convulsion and died that same day. Autopsy about 36 h post mortem (Dr Straub) showed hyperaemia of the organs; the thymus was too large for the patient's age. The hypophysis contained few basophilic cells, both eyeballs were atrophic. The brain showed general hyperaemia but no swelling. At microscopic examination the meninges contained some mononuclear cells, diffusely distributed; many vessels perforating the cortex from the pia also had a slight increase of perivascular lymphocytes. In the brain the small round oligoglial nuclei were often arranged in rows along capillaries in the white matter or deep structures There were no focal perivascular lesions and no demyelination along veins of the diameter generally affected in perivenous encephalitis. These oligoglial nuclei were often surrounded by a small amount of protoplasm No microglial proliferation existed and mild destruction of myelin was found in some parts, where bacterial growth in the brain was evident. These bacteria were sometimes found around vessels (which themselves did not contain the microbes) and in other parts in large areas of the deeper structures. The growth was evidently post mortem, but indicates an existing pyaemic condition

The pathological changes found in this case point to a toxi-infectious condition, occurring shortly after vaccination and probably caused by some bacterial infection No changes were found which could suggest early perivenous microglia encephalitis.

*Case Döring 2*, 1942 Male, 27 years, found dead 13 days after revaccination without any preliminary symptoms Autopsy failed to show any marked changes in the organs, except oedema of the lungs The brain showed the typical picture of encephalopathy oedema, lymphocytic infiltration and slight diffuse proliferation of the glia There was no microglial proliferation around the vessels but some was seen more diffusely in the parenchyma The meninges showed hyperaemia and slight lymphocytic infiltration

*Case Wigand*, 1941 Boy, 10 years old, died 3 days after eruption of a measles rash 3 months earlier he had suffered from acute otitis On the third day after the eruption the condition aggravated, motor unrest and paroxysmal movements were noted, with eye muscle paralysis to the left Patient died the same day Autopsy showed an enlarged thymus, haemorrhagic pneumonia, infectious swelling of the liver spleen and kidneys The meninges were found normal,

without signs of inflammation. Cuffs around vessels were found in the Virchow-Robin spaces, consisting of lymphocytes and plasma cells, with some degree of oedema, but without microglial proliferation or demyelination The vessel walls were hypertrophic in some places.

In his discussion Wigand states that the pathological picture is different from that in the perivenous type of encephalitis, and rather resembles the types found after whooping cough, influenza, etc. Although Wigand says that most cases of encephalitis following measles have a very short incubation period, he considers his case to run a fulminant course. Other cases may show the perivenous type of inflammation. Wigand thinks that status thymico-lymphaticus may have been a factor predisposing to hyperergic reactions and that haemorrhagic pneumonia is also a complication of the measles. According to Wohlwill, encephalitis following measles generally occurs in patients suffering from haemorrhagic pneumonia.

These authors, as shown, do not discuss differential diagnosis in their cases. It is not clear why they do not group them with post-infectious encephalopathies, but rather with post-vaccinial perivenous encephalitis

We will summarize two early Dutch cases (the data on a third child are insufficient) and add the case described by Kokken. It must, however, be borne in mind, in cases of early death, factors may be contributing to a quickly fatal course which are independent of the vaccination, and therefore might complicate the pathological picture.

*Case 9* A boy, 3½ years old, was vaccinated (primary vacc ) on August 6th, 1929, when symptoms of whooping cough were already noted and treated by 4 injections of antiserum On August 16th the child fell ill with fever and had a convulsion during the night Next day stiffness of the neck was noted; Babinski sign on both sides and a soporous condition with high fever (40.8°). He died the same evening. Autopsy of the body showed a normal pustular vaccine reaction, but was otherwise negative The dura mater showed increased tension, the brain was hyperaemic

At microscopic examination the blood vessels were congested, a few red blood corpuscles were found in the Virchow-Robin spaces. No marked perivascular oedema was noted Many blood vessels contained bacilli, which had

in most places already left the vessels to be distributed in the parenchyma. Evidently this was a post-mortem phenomenon, but some foci were found in which polynuclears could be seen around the vessel The patient must have had pyaemia before death

The foci of perivenous encephalitis were typical in most places, consisting of an increase in glia cells, widely scattered in the parenchyma, generally without cellular cuffs in the Virchow-Robin space. This space was often difficult to distinguish The nuclei of the glia cells were round or oval, some had the typical irregular shape of the microglia nuclei The protoplasm showed many processes in various directions. In these foci demyelination was present only in the central parts. No foci were found with demyelination without cellular infiltration, but there were foci in which slight cellular infiltration in the parenchyma existed around a vessel, without demonstrable loss of myelin

In places covering the sulci, the meninges were infiltrated by small and large lymphocytes and plasma cells, many smaller vessels entering the cortex showed some increase in small lymphocytes in their sheaths This was most marked in the superficial cortical layers The vessels of the deeper layers and the white matter were generally normal in appearance

The perivenous foci differed greatly in size, in the smaller foci the glia cells in the surrounding parenchyma were more evenly distributed than in the larger foci, where a concentration close to the vessels was obvious. In these larger foci, more elongated and spindle-like nuclei were present than in the smaller ones. It is very suggestive to regard the larger foci as older than the smaller ones, and then the change in shape of the nuclei and their distribution around the central vessel are important factors in their development. Lymphocytic infiltration was only very small or negligible Haemorrhages were not found in the hemispheres in this case, but around a few thrombosed vessels in the brain stem, erythrocytes were present in the Virchow-Robin space This is thought to be due to the complicating whooping cough

*Case Kokken* This author described the following case in 1937. A boy, 10 years old, who suffered from whooping cough at the age of 5, and subsequently scarlet fever with otitis, showed some progressive mental deterioration He was revaccinated on 15 10 1936 with normal skin reaction and remained in good condition until 26 10 when severe headache started Next day general weakness developed, followed by sleep or a period of unrest Then coma came on, and he died on 28 10, 13 days after the vaccination Pathological examination showed enlargement of the spleen, which was soft, haemorrhages in the lungs,

but no important changes in the other organs The brain was hyperaemic. The meninges were slightly infiltrated by lymphoid cells In the brain a great many perivenous foci of microglial proliferation were seen, mostly very small but some of them already larger. Many of them resembled the embolic type of lesion in size and shape, but they consisted only of microglia cells without lymphocytes or polynuclears, and no vascular changes were found. The glia nuclei were mostly small and round, sometimes slightly elongated, irregular forms were also found, generally lying in an irregular protoplasm. Demyelination was already very marked. No fatty degeneration products In the cortex a few glial nodules were found.

*Case 19* A girl, born 22 6 1930 was healthy before the primary vaccination on 1.11 1940 The pox pustules developed normally, and the child was well until 13.11, when in the evening she became comatose and showed twitching of muscles. She had fever, and perspiration and salivation were increased. The C.S F. sample obtained on 14.11, contained 956/3 cells and Pandy and Nonne reactions were positive She also showed meningeal irritation: stiffness of the neck and Kernig's sign No pareses were noted and the muscular tonus varied Gradually the temperature rose to 40.2° Respiration was irregular, the patient was sometimes cyanotic and she died on 15 11, of oedema of the lungs Myoclonic twitching had been noted throughout the period of observation Autopsy of the body was essentially negative The brain showed some degree of hyperaemia, and was swollen, the brain weight, however, was 1286 g

At microscopic examination the meninges, covering the hemispheres, showed a marked infiltration with haematogenous cells, consisting in many places of a majority of polymorphonuclears. In other places small and large lymphocytes and plasma cells could be found in greater numbers No bacteria were seen. Many vessels, entering the cortex from the meninges, showed hypertrophy of the wall and some slight perivascular infiltration by small round cells. These changes were also found in some vessels in the deeper cortical layers and in the white matter, in which stasis of the blood with clotting was sometimes also seen Then the architecture of the cortex in some places was disturbed by widespread atrophy of ganglion cells; in the occipital cortex more marked in the bottom of a fissure

The three phenomena mentioned (polynuclears in the meninges, vascular wall changes and focal ganglion cell loss), do not pertain to the typical picture of perivenous encephalitis. They probably point to

complication by some other infection, and the results of circulatory deficiency *with hypoxia due to oedema of the lungs* We especially stress this, because the early death in this case, as in both preceding cases, is due to a complication and has no direct connection with the pathogenesis of microglia encephalitis

In the sheaths of some cortical vessels, lipochrome pigment is present in phagocytes and one mesodermal scar was seen adjoining a vessel, probably an organized thrombosis of an artery; the surrounding tissue also contained old blood pigment. No data are available to determine the age and pathogenesis of these lesions

We will now turn to the focal changes (material from the cortex only was preserved). There are a great many subcortical perivenous foci, mostly rather small and sharply demarcated from the surrounding tissue The central vessel is enlarged, with normal endothelial cells or some hypertrophied cells. A few plasma cells can sometimes be found in the Virchow-Robin space, whereas small dark nuclei are scattered in the parenchyma, their number, however, is very small. Probably they are small lymphocytes Polymorphonuclear leucocytes are not seen.

The glial nuclei in the smaller foci are round, oval or slightly irregular, in the larger foci many more irregular forms are seen, often suggesting very active amitotic division Mitoses are very rare It is difficult to differentiate between oligoglial nuclei and the round microglial nuclei, the size of the latter is more variable and generally the nucleus is darker, but often we cannot tell one from the other Demyelination in the foci is quite typical

*Summary* The examination of these *3 early cases* can be summarized as follows

a. The microglial cuffs are already present on the eleventh day after vaccination;
b They gradually increase a little in size and do not all start at the same time, but probably during a short period,
c The microglia cells migrate from the tissues to the vessels and around these, increasing in numbers at the same time, mainly by amitotic division,
d Small lymphocytes or other haematogenous cells play a minor *rôle or are absent; there is no indication that they should precede* the microglia cells, as stated by Lhermitte (1950)

e. Demyelination is not found without microglial increase, whereas the latter may be starting before myelin loss can be demonstrated.
f. *General hyperaemia, slight* perivascular oedema and some lymphocytic infiltration of the meninges are generally present. These findings are about the same as those seen in many cases of encephalopathy, but also in toxi-infectious conditions in patients dying from cerebral diseases.
g. The early death in these cases is probably due to the combination of perivenous encephalitis with other factors: whooping cough, polynuclear exudate in the meninges, pyaemia in the agonal stage.

Comparing the 3 microglial cases with the 3 cases called fulminating, by their authors, it is at once evident, that Doring's case, with death on the 13th day, was not one of perivenous encephalitis, because the microglial changes should have been fully developed at that time but were absent in his case. The cases of de Lange and Wigand do not show any changes that could suggest early demyelination or microglial proliferation, but only the common changes seen in toxi-infectious conditions (this point will be more fully discussed in Chapter 4 on the pathology of postvaccinial death without microglia encephalitis).

In the 3 cases of very early death in microglia encephalitis, the localization of the focal changes was typical of this disease, and no affection of the upper cortical layers was found, which could point to the encephalopathic lesions, as found in the so-called fulminating cases of Doring, de Lange and Wigand Furthermore, death in the early microglial cases was not due to this disease, but to a complicating bacterial infection, and no continuity exists between the time of death in the fulminant cases and in true microglia encephalitis, which we should expect if the two differed only in the acuteness of the disease.

We can therefore add to our summary:

h. The early cases of microglia encephalitis show the fully developed histopathological picture. So-called fulminant cases from the literature must be distinguished, and they are not preceding stages which—if life had not been terminated—would have developed into microglia encephalitis

The earliest cases, described above, suggest that some specific factor acts from about the 9th or 10th day (or even earlier?), causing changes which, in the first period, are generally not sufficiently serious to cause death, unless secondary infections are added as complications, or other noxious conditions are pre-existent.

### 3 *Late stages*

The pathology of the final development of perivenous encephalitis is well known Malamud (1937), v. Bogaert (1950), Lhermitte (1950), Scholz (1957), give the following as essential points: The gradual change of the microglial syncytium into fatty granule cells, with accumulation of these around the central blood vessel and the effluent veins. Generally the foci show a tendency to coalesce and finally the number of infiltrating cells decreases At the same time the astroglia proliferates and may produce sclerosis which, however, is never as dense as in foci of multiple sclerosis. Some authors state that in the later stages lymphocytes are scarce or absent. Most authors agree that perivenous encephalitis is not an intermittent disease.

Puntigam and Daimler (1950) found that, of 9 soldiers who had recovered from encephalitis after primary vaccination, not one reacted to revaccination with cerebral symptoms.

Very few cases have been histologically examined long enough after recovery to allow of a clear insight in the final outcome

Russel and Oddie (1928), in an article on a fatal case of postvaccinial encephalitis, describe a child aged 9 years, dying 26 days after successful primary vaccination The incubation lasted about ten days and the clinical course showed cerebral symptoms with coma, lasting until death Autopsy showed swollen glomeruli in the kidneys, but no encephalitis The brain was hyperaemic, but no cellular perivascular cuffs or microglial infiltration was present The authors considered uraemia a more likely cause of death than encephalitis, which was definitely not found.

This case is sometimes reported in the literature as an example of complete healing of encephalitis, but it is most improbable that encephalitis should have originally existed and have healed out in so short a time. Generally the histological changes are still very marked after 3 weeks.

Herckenrath (1935) described the case of a girl, 5 years old, who had been vaccinated without result in her first year and was revaccinated with good result when 3 years old. She had suffered from a convulsion, when 2 years old and had varicella a month prior to the revaccination. On the 6th day following this, she vomited and again had a convulsion, which resulted in left-sided hemiparesis. A week after the vaccination, vaccine virus was cultured from blood and spinal fluid. The latter contained 10/3 cells but was otherwise negative She had more convulsions, but was considered well 2 months after the revaccination. The hemiparesis gradually disappeared but some speech difficulty remained She died from an intercurrent disease, 1½ years after the revaccination. Microscopic examination revealed many fatty granule cells around the vessels in the white matter but no demyelination was found.

This case, of course, is not conclusive, as the clinical picture of postvaccinial encephalitis was not of the typical perivenous type; more probably it was the vascular, oedematous or haemorrhagic type.

*Case Van Bogaert 2*, 1950 A girl, 9 years old, had at the age of 6 years diphtheria with polyneuritis. Two months later she suffered from measles, with encephalitic symptoms. diplopia, ptosis, nuchal rigidity and pain in the legs In addition, choreatic movements existed in the right arm and she showed a double Babinski sign The C.S F was normal The child gradually recovered without sequelae, and died 3 years later from another type of acute encephalitis Histological examination showed no scars or lesions, caused by the post-measles encephalitis. Clinically, this had been a rather mild case but the diagnosis perivenous encephalitis seems justified.

In his studies on post-measles encephalitis Malamud (1937, 1939) describes the brains of 2 patients, dying 5 years and 4 years respectively, after recovery from the encephalitis. Both cases ran a serious course at first, with hemiplegia and mental retardation as late sequelae Malamud found, at pathological examination, perivenous demyelination still present in the typical distribution, with fibrous glial hypertrophy in the foci and marginal in the spinal cord Microglia cells were no longer found

The contradiction between the cases of van Bogaert and Herckenrath and those of Malamud, can be explained by more serious microglial lesions in the latter's cases, or by a haemorrhagic complication. We will try to show in our material that both explanations may be true in one case or another, respectively.

When examining the literature and our own cases, *we feel that a distinction should be made between patients dying from encephalitis and those cases, in which a complication has arisen, causing death a few days after the beginning of recovery from the original disease.* Some differences in the histological pictures can then be easily explained.

It is also interesting to recall that Grossmann and Humbert (1955) found E.E.G. changes still present a long time after clinical recovery from postvaccinial encephalitis. This probably indicates a rather slow scar formation and absorption of the degeneration products.

Cases of about 3 to 4 weeks' duration have been described by many authors and only a short summary of some of these will be given here.

*Case Wiersma 10*, 1927. Boy, 5 years Primary vaccination. Incubation 12 days. Encephalitis ran normal course, condition improved but on 17th day fever returned, with increasing coma and stiffness of the neck. Death on 21st day Many polymorphonuclear cells were found in the perivascular infiltrations. Many microglial foci were smaller than in his earlier cases. It is very well possible that the child was already recovering from the encephalitis when an intercurrent disease caused a flare-up of the symptoms. This could also explain the polymorphonuclears found by the author.

*Case Suppan 6*, 1937 Girl, 12 years Revaccination with normal skin reaction. On the 11th day fever and clinical encephalitis. Then improvement until the 20th day, when cardiac insufficiency developed and caused death on the 22nd day. Many foci without demyelination but with phagocytes and fatty granule cells Oedema of the brain. Typical microglial foci elsewhere. Evidently this patient was on the way to recovery when cardiac failure caused death.

*Case Perdrau 2*, 1928, mentions that the foci were less cellular than in his case of shorter duration

*Case Leiffer*, 1939 Girl, 5 years. Three days after vaccination headache and abdominal pain, which were progressive Vomited on 13th day, and became somnolent and hypertonic 2 days afterwards Then she showed choreatic movements and remained in this condition until death on the 30th day, due to circulatory collapse Autopsy showed oedema of the organs Foci with marked demyelination and loss of axis cylinders Coalescence of the foci. Many fatty granule cells in the foci and along the vessels No microglial syncytia Some fibrillary gliosis In addition, larger foci of destruction were found which, according to the author, should be considered vascular in origin Subependymal

Fatty granule cells were definitely more conspicuous in the later stages, but were found occasionally on the 11th day in small numbers and in only a few of the foci. We found no indication that granule cells should develop from connective tissue cells, as they do in malacic foci. Their phagocytic activity starts early in the process, and at a certain distance from the central vein.

A migration of the already vacuolated microglia cells from the periphery to the central vein can be deduced from the pictures. The cells are finally found in the vascular sheath, taking the shape of rounded granule cells but often still showing the irregular form of their nuclei (as also stated by Greenfield, 1958). No evidence was found that these cells relay their breakdown products to other cells, as supposed by some authors.

The smaller foci do not show granule cells or fat or fatty acids in the Sudan stain, but we may find elongated and irregular microglial cells with small vacuoles in the protoplasm. This probably means that part of the waste material in the foci is taken up by these cells, and broken down further to transportable products without a stage of demonstrable fat or fatty acids. In the larger foci the amount of degenerated myelin is greater than can be dissolved by microglia (and oligoglia?) and the well known picture of fatty granule cells results. I have the impression that here, as well as in other degenerative diseases, the *invisible way of myelin breakdown* is the more natural process (de Vries, 1958) which, only when insufficient, is aided by breakdown to stainable fat products, which can be found for long periods lying at the site of the focus or along the larger veins.

*Summarizing* the observations on the late stages of the disease, we can say that the smaller foci probably disappear by a process of invisible myelin breakdown, without recognizable scar formation or remaining demyelination. These processes, however, become evident when larger lesions have been present. As will be discussed in the next paragraph, intercurrent diseases, often the cause of death in cases of longer duration, may add additional features to the histological picture and, in cases which ultimately recover, these changes may be the anatomical basis of clinical sequelae.

*4. Influence of intercurrent diseases*

Repeatedly we have had occasion to point out that the occurrence of some peculiar histological picture coincided with additional aetiological factors Proof of a connection between these was difficult to give, but the possibility often struck us. This problem is closely connected with the possible influence, exerted by degenerative or toxi-infectious conditions, existing before the vaccination, on the outbreak of nervous symptoms and their course and histological changes. This will be more fully discussed in paragraph f

We will first discuss the occurrence of *haemorrhages*.

Erythrocytes were occasionally found around dilated veins, but this was not thought to be important, because invariably these cells were quite fresh, evidently an agonal occurrence due to the marked hyperaemia There was no typical localization sometimes they were found in the cortex, sometimes subependymally or elsewhere In our case 9, the child had whooping cough when vaccinated. He also showed a few ring haemorrhages. Cases 38 and 37 both had scars from older brain lesions around the occipital horn, with haemorrhages in this region, and case 37 received other serum injections during the incubation period of the perivenous encephalitis. We also noticed in his brain old blood pigment around some of the intracerebral vessels, suggesting a healed, older lesion Case 41 had rather extensive haemorrhages in the spinal cord, medulla oblongata, and pons, all were fresh and lying in the Virchow-Robin spaces This patient died of pneumonia on the 22nd day Finally larger haemorrhages were found in our case 53, which will be more fully discussed below.

The five cases of our series in which haemorrhage was found, therefore, all show some infectious cause or predisposition which can have caused some damage to the vascular walls, resulting in diapedesis of erythrocytes

The small haemorrhages are caused by an increased permeability of the vascular walls, as part of a nutritional disturbance The smaller foci, consisting of a few erythrocytes, are probably the result of stasis of the blood in the dilated vessels during the agonal stage of the disease They probably have no importance for our conception of the

pathogenesis of the disease of the brain. However, it is known that a small amount of blood, lying outside the blood vessels, can disappear in a very short time without leaving old blood pigment or any reaction of the tissues. It is therefore possible that, when we find these fresh haemorrhages at death, others had already preceded them.

We generally make a distinction between these haemorrhages and the so-called *ring haemorrhages*, although Nordmann (1957) and many others regard the latter as the result of more serious damage to the vessel, but with the same pathogenesis. Here the lesion of the vascular wall is of longer duration and partial necrosis of the perivascular parenchyma ensues, around which the erythrocytes assemble, while oedema and glial reaction can soon be seen in the periphery. This picture, which is well known in a number of toxic encephalopathies (salvarsan, etc.) and is also seen in haemorrhagic encephalitis following influenza and other infections, can develop in a very short time (1—3 days). When the glial reaction around the small haemorrhagic focus is large, the picture may simulate a microglial perivenous focus, as in our case 14 (see Chapter 4c, Figs. 8 and 9). Also Fig. 5 of Crome's (1954) article on encephalitis during an epidemic of influenza suggests such a microglial focus. But very similar pictures can be seen in cases of fat embolism, where certainly no toxic or infectious factor plays a rôle Crome himself considers his case to belong to the group of infectious haemorrhagic encephalitis.

We will now describe *a case in which typical microglial foci occurred besides typical haemorrhagic foci.* We think that the latter are due to concomitant bronchopneumonia.

*Case 53* A soldier, born May 16th, 1923, had no significant illness before his first smallpox vaccination on 7 8 1957. The skin reaction was normal Fever was noted 12 days later, and on 20 8 he was soporous, slightly delirious; he vomited and had some stiffness of the neck. He was then admitted to the Military Hospital* The pupils were equal and reacted to light. No paresis of ocular muscles was found. Neurological examination showed slight general hypersensitivity, no motor disturbances but a positive Kernig sign. The spinal

* Thanks are due to the Director of the Military Hospital in Utrecht for his kind permission to use this case history

fluid contained 903 cells per ml; Nonne and Pandy reactions slightly positive; protein 52 mg/100 ml, glucose 0.92%; gold sol and mastix curves showed only very slight changes. An injection of γ-globulin was given on the day of admission. The E.E.G., taken 21.8, showed bilateral Δ-activity and other changes, suggesting a pronounced disease of the brainstem, with relatively intact cortex. As the temperature was 40.7°, hibernation was started with hydergine, largactil and cold compresses. The respiration became difficult, but improved after tracheotomie. Injections of penicillin and streptomycin were given, also cortisone and ACTH.

In the following days the condition did not improve: respiration was very difficult, with secretion of mucus and oedema of the lungs. Gradually spontaneous respiration stopped and artificial respiration was started. The pulse rate increased and the patient showed cyanosis. The downward course did not react to any therapeutic measures and the patient died of heart failure on 27.8.

*Autopsy**. There was some necrosis of the trachea, probably due to the tracheal cannula, with haemorrhages around it. Then bronchiolitis and bronchopneumonia were found. These were probably due not to viral pneumonia but to a bacterial infection. The lungs were very hyperaemic and oedematous. The other organs showed no important changes. The muscles and the heart were normal at histological examination.

The brain weighed 1695 g (1 month after death, fixed in formalin), the consistency was good. The convolutions were broadened and the fissures less clear. The medulla oblongata and pons were larger than usual and a cerebellar conus was also found. Pia and brain were hyperaemic, and frontal sections showed punctiform haemorrhages.

The detailed histological examination of this case may be interesting because of the long survival of the patient, due to the therapeutic measures. Hibernation, tracheotomy and artificial respiration have probably kept this patient alive at least 3 days longer than in comparable cases in the past. The chief histological conclusion was that microglial foci and haemorrhagic foci existed separately in this brain and that they were seldom mixed.

We will start with a description of the haemorrhagic foci (Fig. 4). The distribution was as follows. *No foci occurred in the cortex or central mass of* the semioval centre. The corpus callosum showed several haemorrhagic foci, especially in the genu and splenium. None in the lateral radiations. Internal

* We thank the Department of Pathology for their kind permission to use the results of their examination.

capsule very few, but external capsule some larger foci around large vessels The thalamus and lenticular nucleus were free, as were the substantia nigra and the subthalamic nucleus (Luys). Some were found in the mammillary body and hypothalamus, and a large accumulation was present in the pes pedunculi.



FIG. 4 Haemorrhagic encephalopathic foci in pedunculus, hypothalamus and corpus callosum. Complication in microglia encephalitis Case 53

The optic tract was not free from haemorrhages either In the pons and medulla oblongata we found some haemorrhagic foci, whereas the spinal cord only contained a few small foci The cerebellar cortex was not absolutely free and some foci were localized near the dentate nucleus in the subependymal white matter Localization in the subependymal glial zone was rare.

*Character of the haemorrhagic foci* We can easily distinguish fresh and older lesions by the condition of the erythrocytes Sometimes, *e g* in the cerebellar cortex fresh erythrocytes were found lying around a small vessel, in its sheath and widely spread in the parenchyma Here, no blood pigment was seen and the vascular or glial structures showed no reaction and no necrosis In

the corpus callosum a small focus with well stained erythrocytes showed demyelination without microglial increase or other cellular response, and no blood pigment.

In the older foci the erythrocytes were partly decolorized with vague contours, and black pigment was present as fine granules. These foci showed partial demyelination, but everywhere myelin sheaths were still seen running between the accumulated blood Glia cells were increased in number, with round or oval nuclei, and some more irregular nuclei of microglia. Lymphocytes and polymorphonuclears were scarce. There was no microglial increase outside the demyelinated area, as is always found in the perivenous encephalitic foci (Fig 5)

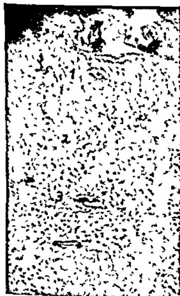


Fig 5a

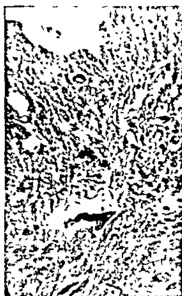


Fig 5b

To compare haemorrhagic and microglia foci a Nissl stain. b Weil stain for myelin of same area in pons 1 and 2 haemorrhagic foci (in b the erythrocytes black), *with very little cellular reaction*

3 Microglia focus around hyperaemic vessel

A few ring haemorrhages with a necrotic centre were found in the cerebellum and in the mesencephalon. Two *haemorrhagic foci were seen in the oblongata*, probably connected with a vessel, showing stasis of the blood. Fatty granule cells were not found in any of these foci, but an astroglial reaction was evident in some of them.

*This description* allows us to consider the haemorrhagic foci as dating from the later period of the disease (no granule cells, early glial reaction) and differing in age. The haemorrhages did not take place in the older microglial foci, and their distribution along the nervous axis was different

*The perivenous microglial foci. Distribution.* In the spinal cord only a few foci were found, but their number increased orally and more foci were present at the level of the pyramidal crossing. Then, in the oblongata and pons, a very large number could be seen sometimes, as in the olives and the reticular substance, occupying nearly the entire field The cerebellar cortex was free, as was the white matter, but the dentate nuclei contained a few large foci. In the mesencephalon all parts showed some lesions. Diencephalon and thalamus *were rather seriously affected, as was the internal capsule, but the lenticular* nucleus was nearly spared. In the corpus callosum several foci were seen, lying separate from the haemorrhagic foci. The centrum semiovale contained foci, mostly in the subcortical parts, the cortex itself was nearly free.

The structure of these foci is about the same as in the other cases. There are small foci with few, widespread microglia cells and without breakdown products or fatty granule cells and other, mostly larger foci, with dense cellular cuffs. These consist of lymphocytes and some plasma cells in the Virchow-Robin space and microglia, mixed with small dark nuclei, outside. Many microglia cells are developing into granule cells and some are found containing fine Sudan-stainable fat droplets This fat is also found in astrocytes and sometimes in vascular wall cells Many pictures suggest that cells are migrating from outside into the vessels and the nuclei of these cells sometimes have the typical dumbbell shape of the microglia, sometimes they rather resemble polymorphonuclear leucocytes.

*Many foci coalesce and seem to* form larger ones, due to infiltration of microglia in the surrounding tissue But when we examine these places in myelin-stained sections, it is evident that practically all the foci remain more or less separate, with a distinct central vessel, thereby still giving an image *differing from that of disseminated encephalo-myelitis*

The majority of the foci did not contain PAS-stainable material, although small droplets might sometimes be seen In the white matter, stained yellowish

brown with the counterstain, pink droplets were very frequent, suggesting that some degeneration of myelin was widespread

In addition to the described haemorrhagic and microglial foci, a more *diffuse glial reaction* was found in many places This could be a very mild form, as slight enlargement of the protoplasm of oligoglia and astroglia, without increase in the number of cells, more marked with hyperplasia of glia cells. These diffuse infiltrations were sometimes found between perivenous foci, but in the cortex they could also be seen in places where no foci were present. Rows of small round nuclei (oligoglia) along vessels were often encountered. They indicate some general reaction of the tissue. Glial stars or "strauchwerk" were not seen in our sections.

*Marginal gliosis*, one of the more characteristic changes in microglial encephalitis, was found in many parts in the subpial region, it was slight in the spinal cord, more conspicuous in the medulla and only very slight in pons, higher parts and cortex. The cellular proliferation consisted, in the more thickly infiltrated areas, of *microglia cells, sometimes together with astrocytes, there* was some degree of demyelination In other areas we gained the impression that this marginal gliosis was due to an increase of the small glia cells (astrocytes), forming the normal outer lining of the nervous system As this form of gliosis is a very common form of reaction, *e g* to meningitis, etc., it must not be confused with microglial marginal gliosis, which is a rare occurrence in other diseases Subependymal gliosis was unimportant in this case, around the lateral ventricles it sometimes formed part of larger foci

The choroid plexuses were normal The meninges showed mild diffuse infiltration with some small and large lymphocytes and plasma cells

*Summary* A man aged 20 years, with no important history of diseases, developed encephalitis 13 days after successful primary smallpox vaccination. Bulbar symptoms soon occurred, for which artificial respiration was started. He died of bronchopneumonia 20 days after the vaccination. Autopsy revealed bronchiolitis and bronchopneumonia.

The brain was oedematous and hyperaemic Microscopically, two types of lesions were found: the typical microglial perivascular foci, with marked demyelination, and haemorrhagic foci with only partial demyelination and no or a mild glial reaction The distribution of these foci was different and no haemorrhages occurred in microglial foci. It is thought that the haemorrhagic foci were the result of the bronchopneumonia, and were not a part of the postvaccinial encephalitis.

## TABLE III

CASES OF POSTVACCINIAL TRANSVERSE MYELITIS

Arranged according to age. Dixon's table not included

| Author or Case No | Age in years | Incubation Enceph. | Myelit. | P. or R. | Autopsy | |
|---|---|---|---|---|---|---|
| Hausmann, 2 | 5 | | 32 | | — | *Soporous before onset. Recovered.* |
| Kaiser Zappert, 17 | 7 | — | 12 | | — | Complete tranverse myelitis. Recovered with sequelae |
| Kaiser Zappert, 19 | 7 | 14 | 14 | | — | Mild delirium. Stiffness of neck. Diplegia *Total recovery.* |
| No 11 | 7 | 14 | 15 | P+ | + | |
| Kaiser Zappert, 26 | $7\frac{1}{2}$ | — | 15 | | — | Paraplegia, anaesthesia. Healed. |
| Henneaux Delcourt | 8 | — | 16 | P+ | | Hereditary predisposition. Paraplegia; recovered |
| Kaiser Zappert, 7 | 9 | — | 19 | | | *Paraparesis day following playing football* |
| No 33 | 9 | 12 | 15 | P+ | + | Death 20 days after vaccination |
| Pette, 1936 | 12 | | | R | + | No data of incubation. Landry syndrome. Multiple foci in brain and cord. Resemblance *to dissem enceph. myelitis* |
| Kramer | 18 | 14 | 16 | P — | — | Started with meningitis? |
| Mage | 20 | — | 14 | R + | — | Received other injections at same time. Myelitis started day after running a race. |
| Strobos | 20 | — | 16 | P — | | Worked on board ship until total transverse lesion Recovery with sequelae. |
| de Busscher, Radermecker | 20 | — | 28 | | — | Vaccin against smallpox and typhoid. *Horseback ride before onset of myelitis.* Autopsy showed microglia encephalitis. |

| Author or Case No | Age in years | Incubation: Enceph. | Incubation: Myelit | P. or R. | Autopsy | |
|---|---|---|---|---|---|---|
| Müller, 2 | 20 | 10? | 11 | P | — | Soldier Subtotal diplegia After one y. still sequelae |
| Gounelle | 21 | 16 | 28 | R — | — | On 16th day mild encephalitis and paresis of legs Partial recovery On 28th day total transverse lesion without encephalitis. Recovered |
| Müller, 3 | 21 | — | 7 | P | — | Soldier. Incomplete transverse lesion Sequelae lasted 2 years. |
| Holbrook | 26 | | 10/12 | R + | + | Syndrome of multiple spinal foci, and blindness Death after 2½ mo |
| Dixon | 27 | — | 32 | P + | — | Soldier Vaccination and typh A + B. Repeated 9th day. 10th day paresis during march Continued service until 33rd day |
| Bakker | 30 | 10 | 12 | R + | — | 10th day hemiplegia with VII paralysis, then paraplegia Probably Heine-Medin infection |
| Müller, 1 | 30 | — | 10 | P | — | Vaccination and typh A + B Total transverse lesion Rapid recovery with mild sequelae |

This case therefore throws some light upon other cases, in which haemorrhages or other signs of vascular wall changes are found, and which are generally described by their author as another kind of lesion due to the same disease. We think that it is erroneous to attribute the changes under discussion to the vaccinia or the factors causing perivenous encephalitis, but that they must be seen merely as a complicating syndrome A consideration of the pathogenesis of post-vaccinial encephalitis should not, therefore, lay emphasis on these changes

*5. Cases with the clinical picture of transverse myelitis*

A number of cases are found in the literature, in which symptoms of transverse myelitis occurred shortly after vaccination, and it seems worth while to establish whether we have to consider them a special group. The typical anatomical changes of microglial encephalitis can be observed in the spinal cord in nearly all cases of postvaccinial encephalitis, most of which do not show transverse myelitis clinically. Symptoms of a slight affection of the spinal cord, however, are mentioned in many case histories.

From our Table XIV we learn that some affection of the spinal cord in postvaccinial encephalitis occurred in all cases in which this was examined by us, and that it was as widespread and as serious in the patients dying early after vaccination as in the cases of longer duration (only numbers 33 and 11 clinically showed transverse myelitis).

However, the incubation time of the myelitis syndrome is not always the same as in encephalitis (8—15 days, see Table III and Fig. 6). The cases reviewed by Dixon (1944) are not included in our first table, all his patients were soldiers, most of whom had simultaneously received other serum or vaccine treatment, and all continued their military training after vaccination. None of them showed typical encephalitis. They probably form a very mixed group. As the pathology of none of these cases is known (4 had a fatal issue), they cannot be classified, but it is evident that a myelitis, starting on the third or fifth day after vaccination, cannot have been the microglial type but must have been due to some other pathological change. Here again, as already said in discussing encephalitis, the clinical diagnosis does not run parallel with the pathological diagnosis. Clinical myelitis includes cases which histologically show necrosis and malacia, or haemorrhagic inflammation, not to be mistaken for the encephalomyelitis we are discussing here.

In the cases in which encephalitis was [illegible] agnosed, preceded the spinal cord symptoms by 0—3 [illegible] is is not

significant difference. As will be seen in Fig. 6, the incubation in several cases lasted longer than is found in microglia encephalitis (see Chapter 6), but only one of these came to autopsy (de Busscher and

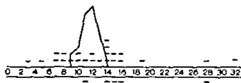



FIG. 6 Incubation of postvaccinial transverse myelitis Above the line the cases of myelitis without clinical encephalitis; below the line cases of encephalomyelitis Drawn line incubation of microglia encephalitis. From the literature.

Radermecker) and the others might well have been myelitis of a different pathology. The case of de Busscher will be presently discussed

In one case (Bakker, 1930), not included in Fig 6, the myelitis was probably part of a Heine-Medin infection, and this case is only mentioned here as it may focus our attention on the possibility that more cases in which no autopsy was performed, could have been acute anterior poliomyelitis, *e g* the case of Henneaux and Delcourt (1954) with 79% polynuclears in the spinal fluid, and Mage's case (1937) with prolonged sequelae. Miller (1953) cites 3 cases of poliomyelitis among a total of 31 soldiers developing myelitis following vaccination. The description of the sequelae after partial recovery is generally very brief, and does not allow us to form a definite conclusion about their pathology.

Why is the incubation time in myelitis longer than in encephalitis?

We could assume that early histological changes in the brain give rise to complaints sooner than lesions of the spinal cord, but it is also possible that the lesions in the cord do not give the picture of transverse myelitis before they become either very numerous or coalescent, with some destruction of the nervous parenchyma (including the axons, which are always found intact longer than the myelin sheaths) Oedema may also be an important factor because the cord, due to the stiff meningeal covering, will be compressed earlier and more seriously

by a developing oedema than the brain tissue, which can more easily expand. But this can only explain cases in which the incubation time is a few days longer than in the encephalitis. In 4 cases of our table, the incubation lasted more than 16 days, an explanation of which it is difficult to give, especially as the pathology is known only of de Busscher's case.

Of the cases of our table, only 5 came to autopsy. In Pette's case no data are given on the duration of the incubation. The case is not regarded by Pette as perivenous encephalomyelitis of the post-exanthematous type, but rather as disseminated encephalomyelitis. *It is possible that the cases in Dixon's table, with an incubation of 19, 28 and 32 days respectively, also belong to this category.* The two cases of our own series and the case of de Busscher and Radermecker, will now be discussed.

*Case 33.* A boy, born 2 12 1936, had been healthy before vaccination on 2. 7. 1947 Pustules developed normally with rather marked skin reaction. General malaise ensued 8 days after vaccination, and on 14 7 headache and dizziness with vomiting were reported This was progressive and stiffness of the neck was noticed the next day. No fever, but positive Kernig sign. C S F. showed increase in cells. There was some weakness of the left leg. On the 15th day paralysis of both *legs and the abdominal muscles was noted, with retention* of urine and faeces At the same time swallowing became difficult and speech defective. He died with high fever on the 20th day after vaccination.

*Autopsy* The brain was not hyperaemic but the meninges were. Macroscopically the brain did not show any abnormality, there was no swelling, no haemorrhage. The spinal cord showed no typical foci macroscopically, but in the 2nd thoracic segment the gray matter did not clearly stand out. Microscopic examination In the spinal cord there was a great difference between the foci. Some seemed to be in regression (thoracic II, ant. column), still with very marked demyelination but only few infiltrating cells These were not accumulated around the central vessel but were lying loosely in the parenchyma. There were no granule cells and the protoplasm was still well developed and showed many processes The nuclei were small and dark, irregular in shape (microglia) In a somewhat larger focus we found some fatty granule cells in *the tissue and also small astrocytes* with clear, round or oval nuclei and a distinct nucleolus

Many larger foci showed the typical arrangement, but everywhere lymphocytes were scarce or absent Granule cells were never found in greater numbers The cord at the lower levels was not hyperaemic but some diffuse oedema was present, the perivascular spaces, however, were not dilated

A very conspicuous change was widespread *chromatolysis of the ganglion cells*, which was most marked in the anterior horn cells but was also found in smaller cells of the posterior grey matter (Fig 7) Not all the cells of one section were affected; normal cells with well developed tigroid substance might be seen near greatly swollen cells with only a small border of tigroid substance peripherally in the cellular body. Other motor cells were pycnotic or showed more general degeneration of the cellular body There was no neuronophagia or small-cell infiltration, as seen in poliomyelitis, and the axis cylinders of the anterior roots were well stained in their central part (inside the cord). This change was found in the lumbosacral cord and at the 11th thoracic level, thor. VI and II, however, did not show these changes in the large nerve cells The significance of this ganglion cell change will be discussed in paragraph e.



Fig 7 Chromatolysis of anterior horn cells Transverse myelitis in microglia encephalitis Case 14 Nissl stain

Marginal gliosis was marked along the anterior longitudinal fissure in the lumbar and lower thoracic cord

The pia of the lumbar cord contained few lymphocytes, except in the anterior

fissure, where dense accumulation of cells was found. Many were granule cells with sharply demarcated protoplasm, without processes but containing many vacuoles (in H.E. stain) and with a rather large and irregular nucleus, which often showed the curious forms found in the hypertrophic microglia of the perivenous foci. Some cells were smaller, not vacuolated, but showing the same tortuous and twisted nuclei. They must also be microglia cells, which have passed the pia-glia membrane before their nuclei became rounded and smaller and the plasma was filled with breakdown products.

The higher thoracic segments (VI and II) showed only slight changes, we found only a few foci and no demyelinated areas, without infiltration. Some veins had a cuff of small lymphocytes, mixed with more irregular nuclei, probably microglia cells which had wandered from the parenchyma to the Virchow-Robin space. There was no marginal gliosis here, and chromatolysis of ganglion cells was also absent. The cord was slightly more hyperaemic than in the lower levels.

The oblongata contained no foci, no important changes were found in the ganglion cells or the subpial tissue. The pons contained some typical foci around swollen veins in the midline, in the dorsal part of the tegmentum.

The cerebral cortex and subcortical white matter were free from foci in the frontal and insular regions, but the occipital lobe contained a number of perivenous foci, mostly localized in the vicinity of the ependyma. These foci were small, with little demyelination and only a few infiltrating cells. Some small lymphocytes were found around vessels, without infiltration in the surrounding parenchyma. The pictures were probably remnants of small foci which had nearly disappeared.

*Summary.* A boy, 10 years old, became ill with general symptoms 12 days after successful vaccination. Cerebral symptoms were never serious, but 3 days later symptoms of transverse myelitis appeared, weakness of one leg having been noted before. He died on the 20th day after vaccination. At histological examination only a very mild affection of the brain, brainstem and upper spinal cord was found, but severe affection of the lower thoracic and the lumbo-sacral cord existed. All lesions had the typical character of perivenous encephalitis; many already showed regression. In addition it was found that there was some oedema of the parenchyma; the vessels in the lower cord were empty (there was hyperaemia at the higher levels), and marked

chromatolysis of a large number of ganglion cells. As this could not be due to an axon lesion, it was suspected to be hypoxic in origin.

*Case 11.* A girl, 7 years old, was vaccinated with good result, for the first time on 4 9 1929 From the start she was not very healthy, but neurological symptoms were not noted before 18. 9 She was then somewhat soporous and had fever. Next day hyperaesthesia was noted and weakness of the legs, which was progressive until total motor and sensory paralysis existed The level of the lesion was diagnosed at the 4th or 5th thoracic segment. Patient died on 26 9 from purulent cystitis and bronchopneumonia.

*Autopsy.* Only parts of the brain and cord were available for examination; the mid-thoracic level was not available. The brain showed only a few lesions, these were small, with typical demyelination, but the number of microglia cells was rather small Evidently these foci had already partially healed. In the pons, many foci were found, most of them loosely built and in regression, with typical microglia cells, very few granule cells and active astrocyte proliferation. In these foci lymphocytes were rare or absent, but in the dorsal part some vessels were found with thick cellular cuffs in the perivascular space, consisting of lymphocytes, large lymphocytes and eosinophile leucocytes There was only a very slight glial reaction around these vessels, consisting mainly of hypertrophic astroglia

At the thoracic level of the spinal cord, very severe changes were found A great many large foci were seen both in the grey and in the white matter. Many still showed the oval shape of the perivascular distribution but large fields, laden with fatty granule cells, lay between them There was total demyelination in the central part, including both anterior horns, but some large ganglion cells were still in evidence Thick cuffs of small and large lymphocytes surrounded many vessels in these foci or in less affected parts. Polynuclears were rare at this level Along the anterior surface of the cord we saw marginal gliosis Proliferating astrocytes were found everywhere and the Holzer stain showed a very dense fibrillar network, especially well developed in the grey matter. Axis cylinders were still present, there was some loss in foci in the white matter and very marked loss in the anterior horns

*Summary* A 7-year old girl died of transverse myelitis, cystopyelitis and bronchopneumonia 22 days after successful vaccination. Encephalitis symptoms had been very mild Typical foci were found in the pons and a few in the hemispheres, all showing healing stages. In the spinal

to explain the segmental clinical syndrome; the higher foci then would not have caused manifest loss of function.

We need not wonder that, in cases diagnosed as postvaccinial transverse myelitis, only few foci are found in the brain because, with marked affection of the hemispheres, the patients are treated in bed and a soporous, or even comatous condition impedes examination of the function of the spinal cord This is well illustrated by the following case.

*Case 41*, a girl of 22 years, became comatous 13 days after primary vaccination Before this, ataxy of the legs had already been noted, and 2 days later retention of urine set in She died of pneumonia, of about 36 hours' duration, 20 days after the vaccination The cord showed, especially at the lower levels, a great many foci, more in the white matter than in the grey horns Granule cells were abundant in some of these lesions, but absent in others, where the microglial proliferation was still intensive. As in our case 33, several anterior horn cells showed chromatolysis, although not as marked as in the other case. Here, therefore, lesions in the cord were not as serious as in the two other cases, clinical examination remained unsatisfactory due to the mental condition of the patient, but would probably have revealed spinal cord lesion if examination had been possible

*Summing up* the aforementioned cases, we can say that the lesions encountered in postvaccinial encephalomyelitis are also present in the cases with the clinical syndrome of transverse myelitis and, although abundant in some segments of the cord, can always be found in the brain also. Many of the foci in the cord are distinctly on the way to recovery, but some become more serious, with more marked destruction of nervous parenchyma without, however, developing into total malacia It is probable that *oedema* of the cord and hypoxia, due to this, play an important rôle in causing the symptoms of total transverse lesion

We gained the impression, that fatty granule cells occurred in large quantities more often in the spinal cord (and oblongata), than in the cerebrum, as an expression of the more destructive character of the lesions in these parts

Intercurrent infectious conditions (purulent pyelitis, pneumonia) probably play an important rôle in this process but there is also reason

authors. B. and K. M. Walthard (1958) think that these fields always belong to some perivenous focus. We cannot agree with this; the occurrence in the upper cortical strata practically rules it out; and the evidence of the large size of these foci seems also convincing.

**d. Marginal gliosis**

This is considered the second most important histological change in perivenous encephalitis because it is present in most cases and rarely seen in other diseases. Since Wohlwill's description in 1928, in a case of measles encephalitis, general attention has been drawn to it and many authors have given accurate descriptions In our material subpial microgliosis was present in 20 out of 23 cases, but even in the others it might have been found if more blocks had been examined The subependymal type was rarer but here too, examination may have been insufficient.

Marginal gliosis is a proliferation of syncytial microglia cells in a very thin layer, directly underneath the pia mater. In the cortex, therefore, it occupies only the superficial part of the molecular layer. The cellular type is the same as that seen around the veins but a change into fatty granule cells is extremely rare. Even in cases of long standing this marginal gliosis still shows the syncytial type. Demyelination is always present, but is rarely as marked as in the centre of perivascular foci.

Its distribution varied from case to case; most commonly it was found along the anterior median fissure of the spinal cord and laterally, dorsal to the anterior horns The subpial white matter of the oblongata, pons and mesencephalon were less often affected, and the cerebral cortex still less Often, but not always, this marginal gliosis was continuous with a perivenous gliosis extending to the surface, and often the impression was gained that marginal gliosis was more frequently seen in places where perivenous foci were found deeper in the tissues. However, we also encountered this marginal gliosis without any perivenous foci at the same level of the cord (*e g* case 53) This is denied by Finley (1937, 1950) and other authors, who consider marginal gliosis to be a continuation of the perivenous foci But our Fig 8 shows a continuous zone of gliosis along both sides of the spinal anterior longi-

tudinal fissure, with only a few perivenous foci in the parenchyma.

The small astrocytes of the most superficial layer and the astrocytes of the white matter may be increased in number; however, a fibrillary gliosis, resulting from hypertrophy of these cells, was not evident in our cases.

We should not confuse the marginal gliosis described above with the *reaction of the superficial small astrocytes* found in cases of meningitis or other irritation. The nuclei of the microglial gliosis have the same irregular shapes as in the perivenous foci: elongated, tortuous, dumbbell-shaped, etc., whereas the astrocyte nuclei are stained lighter, are round or oval, and generally somewhat larger. The protoplasm also differs: the astrocytes show the more regular spider shape, and do not form a syncytium as do the microglia cells.

The occurrence and the importance of *subependymal gliosis* is more difficult to evaluate, because often a perivenous affection in these



FIG 8 Marginal gliosis. Ant fissure of spinal cord. Continuous microglia layer, in many places without connection with perivenous foci. Case 39 Nissl stain

regions, where the veins run parellel to the surface, makes a distinction difficult. Here, too, irritation of the ependymal astrocytes may give pictures which can be easily interpreted as microglial proliferation. We found the subependymal microglial layer in 9 cases and subpial gliosis in 20, but only in 3 cases was it rather marked. In one case (No 45) we found subependymal gliosis in the apex of the occipital lobe, surrounding a solid stalk of ependymal cells, without lumen

**e. Ganglion cells**

It is well known that the ganglion cells generally remain relatively intact in the perivenous foci although, especially in older lesions, some of them may show degeneration (*e g* case 37, a revaccination, in which some of the anterior horn cells show signs of tigrolysis). Some diffuse loss of cells in the cerebral cortex is rather often seen, but this is a very common finding at autopsy when a long agonal period preceded death (stasis of blood in the cerebral circulation and perhaps toxic influences).

We already described the marked *degeneration of anterior horn cells* in two cases of transverse myelitis (No. 33, 41), not connected with focal microglial lesions (this chapter, par. b, 5). This was found in otherwise normal tissue (see Fig 7). Mild degrees of chromatolysis were also present in case 37 in the lumbar anterior horns, without neuronophagia Many typical foci were present at this level of the cord The patient had shown a weakness of the legs, at first suggestive of acute anterior poliomyelitis

The same acute cellular degeneration was described by Pette (1936, p. 271), but in his case, following revaccination, a diffuse glial reaction existed in the anterior horn, as also in other parts of the transverse section. This case is considered by the author to be nearer to the disseminated encephalomyelitis, than to the perivenous type. The pathogenesis of this cellular degeneration is possibly vascular hypoxia, caused by oedema of the cord in cases of longer duration, and more serious destruction of tissue. All cases with this type of ganglion cell degeneration occurred in the spinal cord and in patients with severe clinical symptoms of myelitis Marsden and Hurst (1932) described a

similar degeneration of lumbar anterior horn cells in a case of post-variolar encephalomyelitis; they also regard these changes as not belonging to the usual picture but the pathogenesis remains obscure.

Considerable degeneration of the large cells of the *substantia nigra* was found in our case No. 40. Many cells were ill-defined and sometimes the pigment was lying free, no cellular body remaining visible. This, however, was also considered a reaction to the patient's unfavourable general condition (he had suffered serious brain lesions at a younger age). Similar conditions of the substantia nigra can be seen in postoperative hypoxia cases.

*Abnormal mitotic figures* were described by de Vries (1954) in several cases of microglia encephalitis. They were found to be very numerous in one case, and less numerous in 6 other cases. Generally only a number of small, dark, basophilic granules are seen, lying in a white field, inside a large cell, but sometimes an indication of spindles, as seen in mitotic division, was found. They were considered to be an abnormality of unknown pathogenesis. Rarely we found them in other diseases, *viz.* in a case of typhoid fever and in tuberculoma of the thalamus. Similar pictures were described by Perdrau and Turnbull and McIntosh in postvaccinial encephalitis. Wohlwill (1928) described, in post-measles encephalitis, irregular basophilic granules in the anterior horn cells, which have lost their nucleus. Probably they belong to the same category as our findings. A description of similar bodies by Tinel and Bénard (1923) in a case of ascending myelitis, beginning 5 days after eruption of a rubella exanthema, evidently also belongs to this group. Wyers* recently demonstrated similar nuclear changes in gliomata and discussed their relation to changes, experimentally caused by thiourea injections.

#### f. Complicating aetiological factors

Factors which might influence the constitutional basis on which microglia encephalitis may become manifest, were seen in a number of cases. This aspect of our problem has been discussed by many

* Demonstration in the Dutch Society for Psychiatry and Neurology, 1958. To be published.

authors and may throw some light on the pathogenesis of the process. We will list below the cases which seem to be important in this respect. Of course, our material includes only cases coming to autopsy; whether the same holds true for encephalitis cases which recovered, cannot be stated by us, but it seems very probable.

In 3 cases we found evidence of *preceding disease of the brain.* No 37 showed marked fibrillar gliosis around the lateral angle of the brain ventricle, and phagocytes containing old blood pigment were localized along vessels in the white matter of the brain. The history gave no information about previous trauma or disease.

No. 38 showed a similar picture, but in this case the scar tissue around the posterior horn of one lateral ventricle was much more developed and extended further in posterior direction, where only a closed ependymal stalk was present This case also showed old blood pigment in the sheaths of deep cerebral vessels.

No 40 had even more important lesions. In the left frontal and temporal lobes, old malacic foci were found, with microgyria of the adjacent convolutions Only scar tissue was present; the lesion, probably traumatic, must have occurred early in life. No cause of this disease could be found Microscopically the encephalitis in this case showed, besides the typical picture, glial stars in the oblongata and degeneration of a number of cells of the substantia nigra.

These 3 patients were all soldiers, and nothing abnormal had been noted in them, before the vaccination

A *hereditary predisposition* was involved in one case, No 32, a girl, suffering from clubfeet A brother had spina bifida Evidently we may consider this to be a case of status dysraphicus

*Acquired predisposition* was found in the above 3 cases with old brain lesions, probably of traumatic origin One patient, No 8, was still unable to speak at 4 years of age, no data were available to explain this retarded development.

*Revaccination* may be mentioned here, because in several cases an abnormal picture was seen We saw microglia encephalitis in 2 cases after revaccination (in which primary vaccination had been positive), and in 26 cases after primary vaccination, which should be about the

relation given also for the non-fatal cases. But of the cases of other cerebral affection following vaccination, seven followed revaccination and only 20 primary vaccination (of these 18 were 2 years of age or younger). This will be discussed in Chapter 4.

Our cases of revaccination encephalitis were No. 12 and 37. The former had a typical skin reaction; in the latter the skin reaction came rather early, but was still quite typical. We saw no cases of transverse myelitis following revaccination, as described by Holbrook (1930), Gounelle (1930) and Pette (1936).

Many patients may have suffered from other diseases, known sometimes to cause damage to the brain, but this was not noted down in our material.

An *allergic predisposition* was not evident either in our cases.

An important group is formed by the patients who, *shortly before vaccination or during incubation, were subject to some noxious factor.*

No. 9, $3^1/_2$ years old, had whooping cough when vaccinated and was treated by 4 injections, the last of which was followed by a convulsion; then the encephalitis was noted, which lasted for only one day. Incubation had been 10 days (see case description in paragraph b 2 on early cases).

Angina, of course, is sometimes noted, but in our cases it did not seem to be an important contributing factor

Greater importance should probably be attached to the simultaneous injection of vaccines or antisera against typhoid, cholera, diphtheria or other diseases. This was only noted in our material in one case (No. 37), but probably had been done more often without being recorded. It was the usual procedure in soldiers to give many injections at the same time.

Especially worth mentioning is the possible influence of *mental or physical strain* shortly after vaccination. Case No. 45 was preparing for emigration, which always entails much exertion. A statistical analysis of the occurrence of postvaccinial encephalitis in soldiers, compared with adults of another occupation, might be worth while to give an idea of the importance of mental and physical strain in this group.

Physical strain was evident in cases 39 and 40, two soldiers, who made long bicycle trips on the 12th and 9th day of incubation and who fell ill on the next day and the same evening, respectively. No. 39, dying 2 days after the outbreak of the encephalitis, had a septic condition at autopsy, together with typical microglia encephalitis.

It is interesting to mention the case described by Mage (1937), of myelitis developing the day after the patient participated in a race, and the case of Kaiser and Zappert (1938), of a boy developing myelitis the day after playing a football match, 19 days after vaccination.

It is rather difficult to evaluate the importance of the data given above. We should also bear in mind that in some cases (*e.g* our No 53 and 11) the history specifically states that no important diseases had preceded the vaccination and that the patient had always been of excellent health

We also have to bear in mind the influence that cortisone may have in activating viral encephalitis (discussed in Chapter 4, d).

In the literature, mention is made of the influence of endogenous or exogenous factors predisposing a person to postvaccinial encephalitis. Hutter (1930) mentioned constitutional and familial factors, Sillevis Smitt (1952) also laid stress on the endogenous factors, André-Balisaux (1953) gave several case histories to elucidate the importance of a neuropathic predisposition, of trauma, etc.

An allergic predisposition was noticed by some authors but was absent in many cases

**Summary**

The general picture of perivenous encephalitis, as described by most authors, was also found in our cases. It should be pointed out that the demyelinating microglial foci are only part of the changes seen in nearly all cases. A general mesodermal reaction of the meninges and, in some places, of the vascular wall, was explained as the expression of the systemic disease produced by postvaccinial encephalitis

We formed the conclusion that the typical perivenous foci are primary and not preceded by a vasculo-mesodermal reaction at the site of subsequent microglial proliferation. *When the encephalitis* is not complicated by other (infectious) conditions, the disease is not fatal in the first stages of the foci; when death occurs early in the clinical course, we must admit that the glial proliferation has existed for several days.

The later development and final absorption of the foci, of course, cannot be seen in autopsy material and has to be deduced from cases with death from intercurrent diseases, or after the original lesion has healed out. We reached the conclusion that the smaller foci disappear without leaving a scar or demyelinated plaque because the surrounding myelin fibres group together. The catabolic products in these smaller *foci were broken down by the glia to soluble substances, and fat or* fatty acids were seldom present. In the larger foci, however, we think that the bulk of decomposition products could not be entirely absorbed in this way, and fatty granule cells derived from the microglia were found in larger numbers, transporting the material along the blood vessels, as also seen in other types of destruction. Astrocyte reaction in these foci can cause some degree of sclerosis.

We think that, during the first days of the disease, new foci may develop just as an exanthema increases during one or two days, but this cannot be called progressive involvement. We found some indication that microglial proliferation originated in the parenchyma surrounding the vessel *over some distance, and that these cells* gradually concentrated close to the vascular wall and invaded the adventitial tissue. Increase of these microglia cells occurred mainly by amitotic division. Often the protoplasm was vacuolated, but no sudanophile substances could be detected

When other diseases or affections occur in the course of postvaccinial encephalitis (*e.g.* bronchopneumonia, other vaccinations, etc.) the pathological pictures can be complicated, but this should be separated from the changes of microglia encephalitis.

The picture of transverse myelitis may occur in patients in whom cerebral involvement is not serious. Microscopically, the same lesions

are found as in the cerebrum, but more serious destruction of the parenchyma is often seen. This could be explained by the impeded circulation of blood and lymph as soon as oedema causes compression due to the stiff covering membranes. The possible influence of physical exertion on the outbreak of symptoms is discussed.

*Chapter 4*

# CLINICAL POSTVACCINIAL ENCEPHALITIS DIFFERENT IN PATHOLOGY FROM MICROGLIA ENCEPHALITIS

In this chapter we shall review cases of postvaccinial cerebral complications in which the autopsy findings suggested a process differing from the pathology described in the preceding chapter. It is important for an understanding of the occurrence of various reactions of the nervous tissue to study not only the typical cases but also the negative cases with other types of reaction. The fact that many authors do not pay much attention to this point hampers a general evaluation of the difficulties. A sharp distinction of the various changes found in cases of post-measles encephalitis, however, is made by Litvak (1947). Moller (1949) described these in post-infectious nervous involvement in children. These articles illustrate the importance of a careful description of all cases coming to autopsy.

In the course of our investigation it became evident that in some cases the picture of complete microglia encephalitis was not found but that perivenous foci with demyelination and microglial proliferation existed in the same brains with vascular reactions, although in separate foci. The pathogenesis of these perivenous microglial foci is probably closely related to the pathogenesis of microglia encephalitis but we will group these cases together with the other cases to be treated in this chapter. A full discussion of their occurrence and pathology will be given in Chapter 6, a and b.

Our material, a total of 30 cases, at once suggests that a division into some major groups can be made, which will be discussed in the next paragraphs. Special emphasis is also laid on the so-called encephalopathic changes, the place of which in pathology is still under discussion. Few cases then remain with a pathology differing from the usual pictures (discussed in par f).

**a. Post-infectious encephalitis before and after the year 1923**

It is generally accepted that the wave of postvaccinial nervous complications which attracted world-wide attention, started in the autumn of 1922, gradually increasing in severity until a maximum was reached around 1930 But it is also a well-known fact that nervous complications had been seen before that date and that many cases occurred in the 19th and 20th century which can now be clinically diagnosed as postvaccinial encephalitis.

It will be my object in this paragraph to discuss the problem as to whether microglia encephalitis occurred even before the above-mentioned date, or whether this was really something new, as Spielmeyer (1928) wrote: "die postvaccinale Encephalitis und die Masernencephalitis sind etwas neues".

The literature includes a number of cases referred to by many authors to prove that postvaccinial encephalitis did occur before 1923. We shall discuss these cases below. A distinction between encephalitis and other cerebral complications following vaccination, was rarely made in the last century and in this century before 1925. Convulsions in young children, one of the most outstanding manifestations at this age, were for some authors enough to diagnose encephalitis, whereas others did not think it of sufficient importance to be mentioned.

It is interesting that, according to Kaiser and Zappert (1938), an accumulation of postvaccinial complications occurred in Bohemia in 1802 Among 10,000 vaccinations of babies during that year, 31 were followed by severe convulsions, one by paralysis, one by a soporous condition, all starting 2-16 days after vaccination. Three children died of convulsions. In the years preceding and following 1802 complications were rare.

In 1886, von Barlow described a case of haemorrhagic encephalitis in measles, Freud (1897) mentioned vaccinia as one of the causes of infantile cerebral paralysis Then (1900), according to Bastiaanse (1931), a case (boy, 6 years old) occurred following vaccination but here again convulsions and hemiplegia developed and this case is not accepted as postvaccinial encephalitis

In 1903 a case occurred, described by van Bogaert (1937): a girl, 6 years old, developed poliomyelitis, following vaccination. In the same year complications arose in the Netherlands (Bastiaanse, 1931), but the author did not diagnose them as encephalitis

*A case, described in 1904 by Brissaud and Brécy, of a boy aged 16* dying after 13 days of illness of unknown aetiology, showed multiple perivascular lymphocytes but no microglial proliferation. Some foci showed demyelination and the disease was diagnosed as neuropticomyelitis. It certainly was not a case of microglial encephalitis, as is sometimes suggested in the literature.

Comby (1926) described 3 cases, occurring in 1905, in which serious sequelae followed the vaccination. The age of the children was 4 months, $2^1/_2$ years and 18 months, respectively. In all cases convulsions and vascular syndromes dominated the picture. They do not resemble microglia encephalitis but are quite comparable to the material of younger babies, as given below (par. c).

In 1907 Thausing described a case in which paralyses, resembling poliomyelitis, were still present three months after the onset.

In 1929 Mader described a case occurring in 1912: a child, 21 months old, was vaccinated June 12th; from June 19th on he showed convulsions, became comatous on the 26th but gradually recovered Probably this, too, was an encephalopathy.

In 1912 Gins (1934) observed a girl aged 18 months, developing convulsions on the 12th day after primary vaccination, from which she partially recovered, remaining an idiot. He saw another child, 2 years old, in whom the incubation lasted 12 days; haemorrhagic encephalitis was found at autopsy

Another wave of complications was observed in Holland in 1916 (v. Wayenburg, Koetser, Busch, and others) when, after more than 30,000 vaccinations and revaccinations, many cases of brachial or thoracic neuralgia occurred *Sporadic cases with the same symptomatology* have been observed again after 1925, and are thought to be peripheral in origin These always followed revaccinations.

*It is evident that the cases referred to* (the paradigmata in the literature) dit not show the typical clinical picture, nor at autopsy the

pathological changes of microglia encephalitis. In the literature I found only 4 cases occurring before 1923, in which microglial proliferation in the parenchyma around blood vessels highly resembled microglia encephalitis (a further search of the literature might well disclose more cases).

These cases will be discussed in Chapter 5; a short summary, however, is given here.

1. Turnbull and McIntosh (1926) described a case occurring in 1912, following vaccination. It is generally accepted in the literature as proof that perivenous encephalitis occurred prior to 1923.
2. Krabbe (1913) published the case of a one-year-old child. The aetiology was unknown; the child had not been vaccinated.
3. Marie and Tretiakoff (1921) described a girl aged 16, falling ill on 30 11. 1918, with no known aetiology.
4. Tinel and Bénard (1923) briefly referred to a case of post-rubella encephalitis, occurring in 1921 in a man aged 21.

It is the general opinion that nervous complications following acute infectious diseases have considerably increased in number since 1920—1923. Gins ascribes this to the epedemic encephalitis of 1918—1921 which, when developing after vaccination, should in his opinion adopt a special symptomatology and pathology Other wellknown nervous diseases, *e g* acute disseminated encephalomyelitis, encephalopathies, etc., also increased in numbers (Gins, Bastiaanse, Lucksch, Turnbull and McIntosh, v Bogaert, Scholz, Kaiser and Zappert).

That the perivenous type of encephalitis did not occur before 1923 is stated by Spielmeyer and accepted by Pette (1936), who found no histological proof to the contrary in the literature, and also by Walthard and Walthard (1958)

In measles Wohlwill (1928) stated that, before 1925, encephalitis following this disease was nearly unknown, but increased in frequency following the pandemic of v Economo's disease. Musser and Hauser (1928) report the same condition in the U S, where encephalitis

following measles infection was formerly unknown, but was reported in 1927 in various States.

C. de Lange (*1943*) *gives 1 in 1,000 as an average* for the more serious complications in the course of measles—a rate certainly much higher than before. Litvak (1947), who also estimates the number of measles *encephalitis* cases at that *time* at 1 in about 1,300, says that, during 1902—1924, only 2 of 2,000,000 cases of measles had cerebral complications in England.

The nervous complications that followed vaccination before 1923 are discussed *in a number of reports and articles.*

In 1902 a commission was formed in the Netherlands to report on the complications of vaccination against smallpox. Ninety per cent of the practitioners returned the completed questionnaire. Following 2½ million vaccinations, skin reactions and erysipelas were most common, then abscesses and other septic conditions. Meningitis occurred twice; in both cases the tuberculous type was diagnosed. No other cerebral complications are reported. Convulsions did occur but were not considered *a complication of the vaccination, although some reports* state that they occurred more frequently after vaccination than without it. Vaccination at that time in the Netherlands was done mostly in children aged 4—6

The English *Report on Vaccination* (1928) notes that, from 1911 to 1925, 3.7 million vaccinations were done in children under 1 year of age, with 133 deaths, and 600,000 in older persons, with 15 deaths. Death was due to convulsions in 26 cases, to meningitis in 4, to haemorrhagic encephalitis in 1 (in 1923) and to acute encephalitis in 1 (1923)

In contrast to the above data, the dangers following vaccination increased after *1923. Bastiaanse (1931)* states that in 709,918 primary vaccinations, 54 cases were reported with untoward complications which were certainly not postvaccinial encephalitis, and an additional 59 cases which were probably not. *The percentage of cases* with a fatal outcome was about 30. His material, however, is not uniform and no definite conclusions ca[illegible] ...fore be m[illegible]

TABLE IV

DEATH DUE TO PRIMARY VACCINATION

| | *Year* | *Prim. vacc.* | *Deaths* | *Frequency* |
|---|---|---|---|---|
| Dutch Commission | ±1890–1901 | 2 500 000 | 6 | 1.416 000 |
| English Report | 1911–1922 | 3 700 000 | 133 | 1: 27 000 |
| Dutch Report 1932 | 1924–1928 incl. | 709 000 | 38 | 1: 21 000 |

The Dutch Commission excludes from statistics on death due to vaccination cases of tuberculous meningitis or activation of other diseases, whereas these are included in the English statistics Another point which impedes conclusions is the difference in age at which vaccination was generally performed.

A few words may be said about the *significance of convulsions* as a sign of post-infectious cerebral disease.

Convulsions followed vaccination in 1802 in Bohemia (Kaiser and Zappert, 1938) in a rather large percentage: 31 in 10,000 vaccinations (1 : 322), with 3 deaths (1 : 3,300).

According to Julius (1938), convulsions were given as the cause of death during the first year of life of 1,041,493 children during the years 1931—1936, as high as 1916 (1 · 543) The rôle of vaccination is not especially stated

Bastiaanse found convulsions in his material of pathologically or clinically certain cases of postvaccinial encephalitis in 48 of 138 cases (1 2.8).

The English *Report* (1928, p. 41) states "Convulsions are occasionally met with in the course of vaccinia as in other febrile conditions, but it was not until 1923 that certain other manifestations appeared".

The material discussed in this paragraph is rather suggestive of the following *conclusions* (see also Table XI, p. 141).

(1) Typical fully developed microglia encephalitis following vaccination has not occurred before the autumn of 1922 Turnbull's case of 1912 is atypical in many respects.

(2) The pathological picture of perivenous microglial foci can occur sporadically following vaccination (1 case), rubella (1 case), or without definite aetiology (2 cases), and is also rarely met with, after 1923, without previous vaccination or other exanthematous disease.

(3) Convulsions in young children apparently do not occur more frequently after 1923 than they did periodically before that date. They should therefore not be considered a danger inherent in postvaccinial encephalitis, which only occurred from 1923 on

According to Marchand and Ajouriaguerra (cited by Rademecker, 1958) three main groups of convulsions should be distinguished: "Convulsions isolées fébriles" with a good prognosis without sequelae; "convulsions des spasmophiles" and "convulsions répétées", often progressing into epilepsy.

There is, however, some evidence that an encephalopathic reaction following vaccination (haemorrhagic, lymphocytic, toxic) increased in frequency after 1923, especially in very young children.

Death from microglia encephalitis still periodically occurs in the Netherlands when mass vaccination is performed (see Fig. 9), whereas death due to postvaccinial nervous complications other than this type, continues to occur more regularly. The figure could even suggest that the relation of encephalopathy to vaccination is much less important than it has been supposed to be.

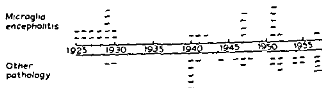



FIG 9 *Frequency of microglia encephalitis compared with cases with other pathology, in the years 1925 to 1957. Dutch autopsy cases*
From 1930 to 1939 vaccination was nearly stopped. In 1940 a new vaccination law was passed In 1947 mass vaccination because of smallpox eruption in Tilburg In 1951 mass vaccination because smallpox occurred in Breda.

**b. Children under 2 years of age show no microglia encephalitis**

A systematic examination of the Dutch cases of postvaccinial complications has revealed the interesting fact that microglia encephalitis does not occur in infants in their first and second year of life. In a survey of the literature the same observation was made. A great number of cases have been reported but, whenever an adequate description was given, another type of pathological reaction was found Many of these cases were diagnosed as postvaccinial encephalitis; others as encephalopathy and only in a few cases did the author especially note that they belonged to the perivenous type or were an initial stage of perivenous encephalitis. Sometimes other writers interpreted these cases as such These cases will now be discussed in some detail (Turnbull, 8; Schurmann, 2, Doring, 1; Jacob; Baló, 4; Zulch, 10; Schleussing).

*Case Turnbull 8*, 1928. A boy, 3 months old, fell ill on the 10th day following vaccination and died on the 25th day Turnbull considered this as a subacute case Pathological examination showed oedema and hyperaemia of the brain, no haemorrhages There is a very diffuse mild increase of glia nuclei In the left pulvinar we found a focus with oedema and old as well as fresh erythrocytes in the parenchyma but this was not perivascular. There was some hypertrophy of the astrocytes The lumbar cord showed perivascular oedema Fatty granule cells were present in the vessel sheaths in various sections and could be followed into the subarachnoid space The haematoxylin and eosin stains showed no demyelination

Turnbull groups this case together with his other cases (of older persons) as postvaccinial encephalitis We would now call it an encephalopathy, and it certainly does not belong to the microglia encephalitis group, as is sometimes contended in the literature

*Case Schürmann 2*, 1928 A child of 11 months acquired varicella at about the time of vaccination It died 12 days later of bronchopneumonia The vaccination pustules developed normally. On the 8th day the child had convulsions Autopsy showed fresh granulations on the mitral valve The meninges were slightly blurred at the base, the ventricles dilated Only one block was microscopically examined (probably paraffin embedding and haematoxylin-eosin stain) Schurmann mentions protoplasmic glia cell proliferation around the

essels, but expressly states that the case had been insufficiently studied to use or a description. His first case, a child 6½ years old, showed typical microglia encephalitis, and Schurmann gives a very good description of it, using this case or his description of postvaccinial encephalitis

As glial hypertrophy occurs after small haemorrhages or around small, necrotic foci, and as demyelination was not noted, the second case of Schurmann does not prove that microglia encephalitis can occur at a very early age.

*Case döring 1*, 1942. A child, 15 months old, was vaccinated 28.9 and fell ill on ..10 with vomiting. 7.10 he had convulsions; the temperature rose, he became omnolent and died the following day. The spinal fluid showed 74/3 cells. Autopsy showed hyperaemia of the brain and mild lymphocytic infiltration of he meninges The parenchymal vessels were engorged with blood and sometimes urrounded by oedema. Some plasma cells could be found and lymphocyte uffs were present around a number of vessels. Ganglion cells were found to e practically normal.

Doring considers this to be an initial stage of perivenous encephalitis We cannot follow him here. Firstly, in older children dying on the leventh day after vaccination, the typical picture of demyelination nd syncytial microglia can be seen (*viz.* our case No. 9). Then the hanges in Dorings case, as in many cases of encephalopathy with eath around the 10th day, were widely distributed in the brain, not n foci with large stretches of normal tissue between them. They are ypical of encephalopathy and there is no proof that these changes hould have changed into perivascular microglial foci if the child had ved. We shall presently discuss the problem of fulminating cases more extensively.

A case briefly mentioned by H. Jacob (1956, case 1), should be listed ere, although the description only states death at 8 months, following mallpox vaccination, with "Lymphocytärer perivenoser Encephalitis mit laminarem Oedem der U-Fasern und beider unteren Rindenchichten". Probably this was not a microglia encephalitis b ascular accident. The name perivenous encephalitis is used by lso for encephalo-myelitis disseminata

Baló's case 4 is a child, 2 years old, who died 17 days after

tion. Focal perivenous haematogenous cells were present; no microglia is mentioned, but demyelination was found. It is not certain that this might have been the youngest case of microglia encephalitis; it could well have been a haemorrhagic or embolic type

A case described by Zulch, 10 (1954) as typical para-infectious perivenous encephalitis certainly does not conform with the picture Spatz gave as typical when he coined the name, and in the sense it has been used by many later authors. A child, 16 months old, fell ill following a common cold The child had not been recently vaccinated Death on the 5 th day of illness. Histopathology showed predominantly lymphocytic perivenous infiltration and early demyelination. The latter was probably caused by the oedema found in these cases.

Schleussing (1953), in a preliminary communication, reports on 14 cases in children 6 months to 1½ years old, with acute cerebral symptoms following vaccination in 4 to 16 days All cases showed serous exudation without demyelination or microglial reaction Schleussing considers his cases to be an early phase of perivenous encephalitis, but his findings are the same as in our cases in young children and we cannot accept his explanation.

Table V gives a list of the autopsy data of 33 cases of

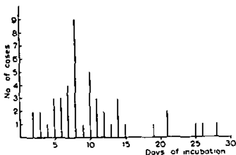



FIG 10 Incubation of cases of postvaccinial C N S complications other than microglia encephalitis Children 0 and 1 year of age Dutch cases and the cases from the literature, mentioned in this treatise

## TABLE V

CHILDREN UNDER 2 YEARS OF AGE, POSTVACCINIAL DEATH

Cases from the literature, with autopsy findings

| *Author* | *Age in months* | *Incubation* | *Death days after vaccin.* | *Clinic* | *Pathology* |
|---|---|---|---|---|---|
| Turnbull VIII | 3 | 10 | 25 | | *Oedema; hyperaemia; haemorrhag.* No glia prolif.; granule cells around vessels. |
| Eckstein, 37 | 4 | 11 | 15 | | Perivasc. cell. infiltr.; Diffuse cell infiltr.; Ggl cells degenerated, Glia increased |
| Report Vaccin. | 4 | | | | Acute cerebral oedema. Bronchopneumonia. |
| Lawler | 5 | 12 | 16 | | Oedema of meninges and brain. |
| Eckstein, 90 | 6 | 8 | 9 | | Oedema of meninges. No encephalitis |
| Gins, 11 | 6 | 21 | 33 | | TB meningitis. |
| Eckstein, 47 | 7 | 11 | 15 | | C.S.F. polynuclears In brain perivasc. infiltration |
| Eckstein, 99 | 7 | 7 | 10 | | Hyperaemia; no encephalitis; |
| | 7 | 8 | 9 | | C.S.F. with pneumococci. |
| Gins, 13 | 7 | 8 | 9 | | Oedema of meninges, no encephalitis |
| Gins, 14 | 8 | 8 | 10 | | Pneumococcic sepsis, no encephalitis |
| Dolgopol | 8 | 15 | 16 | Excema Vaccinia general | Oedema, thromboses; no glia hypertr.; no demyelination perivascul. infiltrates. |
| Granier Gate | 10 | 13 | 15 | | No macrosc. lesion of C.N.S. |
| v. Bogaert | 11 | 28 | 42 | | Septic condition *Slight* encephalopath. changes |
| Eckstein, 101 | 11 | 10 | 43 | | No postvacc. encephalitis Probably TB |

| | | | | | |
|---|---|---|---|---|---|
| Schürmann, 2 | 11 | 8 | 12 | Bronchopneum. Varicella; convulsion | One haemat.-eos. s[illegible] glia around vessels. I[illegible] data |
| Baló 2 | 12 | 14 | 15? | | Thromboses of vesse[illegible] and body. |
| Eckstein, 95 | 12 | 21 | 28 | | No encephalitis, hydro[illegible] |
| Goeters, 2 | 12 | 7 | 7 | | Venous hyperaemi[illegible] negative |
| Rohmer, 1 | 12 | | | | Oedema; hyperaem[illegible] leuco- or lymphocytes |
| Rohmer, 2 | 12 | | | | Oedema; hyperae[illegible] leuco- or lymphocytes |
| Bentivoglio, 3 | 13 | 8 | 9 | | Poliomyelitis |
| Eckstein, 46 | 14 | 4 | 10 | | Hyperaemia, oedema [illegible] filtrat. Brain micr[illegible] |
| Doring, 1 | 15 | 7 | 10 | | Hyperaemia, oedema [illegible] cytes perivascul. more [illegible] white matter. |
| Retter | 15 | | | | Meningitis and oedema, no glia proliferation |
| Bentivoglio, 1 | 16 | | | | Focus in pons, diffuse encephalitis, not specified |
| France | 18 | 26 | 28 | Vaccinia gen. | Haemorrhagic encephalitis |
| Granier, Valette | 18 | 14 | 23 | Vaccinia gen. | Haemorrhagic encephalitis |
| de Vries | 18 | 3 | 14 | | Epidemic encephalitis |
| Eckstein, Esser | 20 | 6 | 13 | Toxi-infect enteritis | Ggl cells very diffuse degener Glia diffuse hypertrophy, vessel endothelia swollen |
| Martinsohn | 23 | | | | Vaso-glial prolifer., no demyelination |
| Balo, 4 | 24 | 6 | 17 | | Oedema of brain, perivascul lymphocytes, plasma cells and polynuclears Fatty granule cells, demyelination, no microglia mentioned |
| Jacob | 24 | 8 | 10 | | Lymphocytic infiltr.; exsudative syndrome |
| Kaute | 27 | 11 | 15 | | Haemorrhagic encephalitis |

plications, E.E.G. changes indicating a subclinical cerebral affection but none of these occurred in children under one year of age.

During a measles epidemic in Greenland (Christensen *et al.*, 1952–1953) in a population without immunity (4,262 persons out of the total population of 4,269 acquired the disease) 6 cases of encephalitis occurred, all in persons 2 years of age or older. Sudden death in the prodromal stage occurred in 2 children out of 321 cases; in older persons in about 0.6%, *i.e.* about the same frequency.

*To summarize*, we can state that the very young brain does not react to vaccination or exanthematous diseases with demyelinating foci and microglial proliferation, as the older brain sometimes does. This is probably not due to an insufficiency of the glia. A different chemical constitution of the myelin may play a rôle, but cannot be the only factor. As there is no difference in the histological reaction of the very young and the older brain to viral infections, it is improbable that perivenous encephalitis be caused by a virus.

Perhaps a sensitization to allergic reactions has not yet taken place. Most probably several factors act together to protect the infantile brain from the demyelinating reaction.

In other respects, however, the baby brain can react in the same way as the more developed brain to typical neurotropic virus infections, to toxi-infectious conditions, to vascular accidents and hypoxia. It remains a point of further research whether the reaction to other demyelinating conditions in the very young differs from that in the older brain.

### c. Revaccination cases and their pathological substratum*

Many authors have published cases in which encephalitis, following revaccination, showed a picture other than the expected perivenous type. *But it was Bastiaanse who for the first time* (1949, 1955) *stated that,*

* The literature has been reviewed by Mrs. Zwanikken, M.D., in search for autopsy cases in which the skin reaction showed a partial immunity. About 1400 articles were available, and of several articles only brief references or abstracts could be obtained. We feel certain that no case in which exact data about the skin reaction to the vaccination and an accurate autopsy report are given, has escaped our notice. A diagnosis "typical postvaccinial encephalitis" has been listed as insufficient for our purpose.

*in all cases known to him, in which the skin reaction to the revaccination showed partial immunity, microglia encephalitis was not found at autopsy* and the incubation time and clinical course might also show differences from the usual picture.

That, however, microglia encephalitis has been found following revaccination, has been described by a great number of authors. It is well established that revaccination, followed by eruption of normal pustules, can be followed by perivenous encephalitis, though in a much smaller percentage than after primary vaccination. We have examined 3 cases illustrating this fact, all of which showed normal pustular skin reaction to the revaccination.

In 8 of our cases the skin reaction to the primary vaccination had been negative. We have included these cases in our revaccination paragraph, because many authors think that, even without a reaction of the skin, the vaccinia virus may invade the body and give rise to the formation of antibodies (Eckstein *et al.*, 1930). Van Bogaert says (1947) that, when encephalitis follows, the brain may take over the function of the skin to prepare immune bodies and that the encephalitis may be a manifestation of the disease vaccinia, localized in the brain.

Rehsteiner and Wiesmann (1949) demonstrated antibodies to vaccinia in the serum of a child aged 1½ years, who had not shown a skin reaction to the vaccination but developed encephalitis 10 days later

A case described by Eckstein, Herzberg, Kremmer (1930) seems rather conclusive A child aged 15 months is vaccinated without apparent result Vaccination is repeated 14 days later and an early skin reaction results Five days later the child develops convulsions, fever and a soporous condition After injection of reconvalescent serum the child recovered without persisting symptoms The authors state that, in other cases also, signs of immunity may follow an apparently unsuccessful vaccination The case described by Herckenrath (1935) (see Table VI, group I, p 86), is perhaps also an example of this assumption, as pathological examination, two years after recovery, did not show signs of healed microglia encephalitis,

and as the incubation was shorter (7 days) than usually seen in histologically verified cases.

We have listed the *cases of revaccination* on which sufficient data were available (Table VI, p. 86), and divided these cases into 3 main groups: one with normal skin reaction to the revaccination; the second group with accelerated or very mild reaction, and a small third group in which no data about the skin reaction could be obtained. The first group (I A—D) includes all pertinent Dutch cases and a certain number chosen at random from the literature (this number could be easily increased). Group II (II E—H), with partial immunity reaction, comprises all cases in which sufficient data on skin reaction, clinical course and autopsy findings are given, from the Netherlands

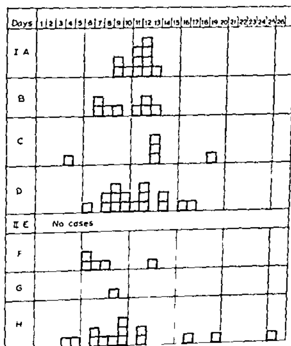



FIG. 12 Incubation time in the groups of revaccinations.

and from the literature. In the third group are listed the cases with insufficient data about the revaccination skin reaction

*Group I A*

When revaccination gives rise to a normal pustular skin reaction, a certain number of patients will react with postvaccinial microglia encephalitis. We have listed 11 cases The incubation time (see Fig. 12) is the same as in postvaccinial encephalitis following primary vaccination, the clinical course and the histopathological picture do not significantly differ from the well-known description of microglia encephalitis. No difference is noted between the cases with a positive and those with a negative skin reaction to the primary vaccination. Our number of cases is too small to make an evaluation of the frequency with which encephalitis follows successful revaccination

Probably the percentage is less than that following primary vaccination.

*Group I B*

Eight cases have been accurately described in which revaccination was done with good result and an ensuing encephalitis did not show the microglial type. A short description of each case is given below. Several facts attract our attention The age distribution (Table VI) varies much more than in primary vaccination; also the incubation time is irregular and the wide variety of changes found in the brain may lead to the conclusion that this is not an homologous group but merely a collection of cases of very different aetiology and pathogenesis

*Groups I C and D*

The *groups C and D* are combined here, because they show an irregular spreading of the incubation time They probably comprise cases of perivenous encephalitis together with cases of different pathology. The variation in incubation time resembles that found for encephalitis

## TABLE VI

CASES OF REVACCINATION

| *Case No.* | *Age in years* | *Result primary vaccin.* | *Incubation in days* | *Survival after vaccin.* | |
|---|---|---|---|---|---|
| I. NORMAL PUSTULAR SKIN REACTION TO THE REVACCINATION | | | | | |
| A. *Microglia encephalitis* | | | | | |
| No. 5 | 3 | P— | 12 | 19 | |
| No. 12 | 13 | P+ | 9 | 14 | |
| No. 37 | 19 | P+ | 12 | 19 | Chol. Typh. A+B inj. at time of revacc. *Old blood pigment in brain.* |
| Turnb., 3 | 22 | P— | 9 | 14 | Case of 11.1922 Blood in spin. fluid Bronchopneum Myelitis, meningo-encephalitis |
| Lucksch | 14 | P— | 10 | 20 | |
| *Sjov* | *23* | *P?* | *13* | *16* | *Blood Wass + Clinic. poliomyelitis,* ascend. paral. Typical demyelination |
| Thom | *12* | P+ | *12* | 14 | |
| *Bras* | *12* | P— | *11* | *14* | *Convulsions C.S F. 500 cells.* |
| Kok. | 10 | P+ | 11 | 13 | Mentally backward. |
| Zier. | *16* | P? | 12 | 21 | Had eczema, this infected Vacc gen *furuncul Microscopically not quite typical* |
| Supp | 12 | | 11 | 22 | Death from heart failure Microsc not *typical* |
| B *No microglia encephalitis* | | | | | |
| No 42 | 26 | P- | 6 | 8 | *Diabetes Embolic encephalitis* |
| No 18 | 62 | P- | 11 | 15 | Clinic general paral ? Microsc. diff changes |
| No 43 | 56 | | 8 | 9 | Death due to myocarditis *Senile brain* atrophy |

| Case No. | Age in years | Result primary vaccin. | Incubation in days | Survival after vaccin | |
|---|---|---|---|---|---|
| Sjov., 2 | 34 | P+ | 9 | 11 | No demyelin Thrombosis of veins. Inflamm of vessels and adventitia |
| Herck | 3 | P— | 6 | 13? | Convulsions; hemipares Recovered. After 2 y. no sequelae found. |
| Ramon | 12 | P— | 12 | 18 | Haemorrh. enceph. Many small cells could have been microglia |
| Dor. | 27 | | 13 | 13 | Found dead Oedema of brain |
| And | 39 | | 12 | 16? | Cerebral thrombosis |
| *C. Death without autopsy report* | | | | | |
| Kaut., 2 | 12 | | 13? | 20 | Cerebral oedema; type of encephalitis doubtful. |
| Mor, 1 | 10 | | 13 | 17 | Coma, convulsions. |
| Mor., 2 | 10 | | 13 | 16 | Coma, convulsions. |
| Busch Eck, 49 | 12 | | 4 | 8 | Motor unrest |
| No 44 | 68 | | 19 | 24 | Bulbar paral. perhaps poliomyelitis. |
| *D Recovered* | | | | | |
| Mad, 2 | 11 | P+ | 6 | | Typical course, could have been perivenous encephalitis |
| Mad., 4 | 2 | P— | 10 | | Probably perivenous encephalitis |
| Rooz | 7 | | 10 | | Sopor, vomiting, positive Babinski |
| Gort | 57 | | 9 | | |
| Siss | 29 | P+ | 9 | | Complete recovery |
| Dene | 11 | | 11 | | |
| Goun. | 21 | | 16 | | Myelitis, healed. Relapse 27 days after vacc., recovered |
| Kaut | 13 | | 12 | | Paralyses resembling ac. polio Partial recovery |
| Paul | 7 | P+ | 12 | | R±, partial recovery |

| Case No. | Age in years | Result primary vaccin. | Incubation in days | Survival after vaccin. | |
|---|---|---|---|---|---|
| Comb., 16 | 10 | | 8 | | Meningism, coma, pos. Babinski; pareses, recovered. |
| Comb., 17 | 10 | | 6 | | 12 days after vaccin. subtotal paralysis; recovered. |
| Lere. | 10 | | 14 | | Paralyses of legs; after 13 d recovered. |
| Mage | 20 | P— | 14 | | Had typh. inj., clinical myelitis |
| Dunn | 21 | | 17 | | Mentally clouded; flacc. paral. after 6 mo still sequelae. |
| Mado | 60 | | 8 | | Zoster 4 d. after onset enceph. Meningo-encephalitis. |
| Leifer | 20 | | 10 | | Vaccin during typh. inj. series Parkinsonism. |

II. IMMUNE SKIN REACTION TO THE REVACCINATION

E. *Microglia encephalitis*

No cases

F *Autopsy shows another pathology*

| | | | | | |
|---|---|---|---|---|---|
| No 13 | 13 | P+ | 13 | 15 | Small number of foci, with polynuclears; no demyelination. Pyaemic lesion |
| No. 14 | 13 | P+ | 6 | 9 | Epilepsy from childhood Imbecil Haemorrhagic lesions. |
| No. 15 | 29 | P- | 7 | 16 | *Massive diff demyelination, haemorrhages, atypical myelin transport.* |
| Baron | 28 | | 6 | 16 | *No cellul infiltrat., no demyelination* |
| No 56 | 21 | P—? | 8 | 0 | 6th day ataxia, then delirium Encephalopathy with haemorrhages |

G *No autopsy*

| | | | | | |
|---|---|---|---|---|---|
| v. B B 11 | 16 | P+ | 9 | 11 | 5th—9th day malaise, then paralyses Probably poliomyelitis. |

| *Case No.* | *Age in years* | *Result primary vaccin* | *Incubation in days* | *Survival after vaccin.* | |
|---|---|---|---|---|---|
| II *Recovered* | | | | | |
| Berg | 6 | | 7 | | Myoclonia, sopor, later Parkinsonism |
| Bak | 30 | | 10 | | Hemiplegia, then quadruplegia Probably poliomyelitis |
| Bos | 54 | | 10 | | Zoster eruption, no other encephalitis sympt |
| v B B 2 | 26 | P+ | 4 | | Kernig pos , Babinski |
| v B B 3 | 6 | P+ | 17 | | Rigidity of neck 25th d paralysis of arm Probably poliomyelitis |
| v B B 4 | 10 | P+ | 20 | | Paralysis one arm, Babinski pos. Possibly poliomyelitis. |
| v. B. B 6 | 30 | P+ | 10 | | Convulsion, mentally disturbed, sequelae Probably enc myel dissem |
| v B B 8 | 16 | P+ | 12 | | Paralyses with atrophy 9 mo in bed. Probably poliomyelitis |
| v B B 10 | 7 | P+ | 7 | | Flaccid paralysis legs Probably poliomyelitis |
| v B B 12 | 35 | | 8 | | Kernig, Babinski |
| Noord | 31 | P+ | 9 | | One day mentally disturbed Heart bloc Next day recovered |
| Eckst | $1\frac{1}{4}$ | P— | 5 | | Convulsion, recovery |
| Jaub | 22 | P+ | 26 | | Kernig pos , later, 26th d poliomyelitis |
| Wolman | 39 | P+ | 12 | | 14th d zoster eruption and encephalitis Recovery with sequelae |

III NO DATA ABOUT REVACCINATION REACTION

| | | | | | |
|---|---|---|---|---|---|
| Car | 16 | | 13 | | Strabismus, sopor, recovery in 5 weeks. |
| Gins | | | | | Haemorrhagic encephalitis |
| Miller | 22 | | 3 | | Hemiplegia, aphasia After 16 mo focal epilepsy |

| Case No. | Age in years | Result primary vaccin. | Incubation in days | Survival after vaccin. | |
|---|---|---|---|---|---|
| Goet. 14 | 14 | | 9 | 11 | Haemorrhagic encephalitis |
| Goet. | 12 | | 9 | 16 | Perivascular focal encephalitis |
| Pette | 12 | | | | Clinical Landry. Path resembling enceph. myelit. dissem |

following primary vaccination, in cases in which microglia encephalitis was excluded by post-mortem examination (Fig. 19, see p 137).

*Group II E*

Microglia encephalitis in revaccination cases with immune skin reaction. *No such instance has been found in the Dutch material or* in the literature. A search of the literature to this purpose was rather depressing, because very few articles gave sufficient data about the skin reaction and the microscopic picture. Only one case from the literature (Baron, 1929) could be used in addition to the 4 Dutch cases of group F The assumption would seem justifiable that, when a case is considered interesting enough to be laid down in the literature, the author would mention the type of skin reaction to revaccination if it were not normal, and that therefore few cases could have escaped our notice.

We shall not try in this chapter to give an explanation of the very *important fact that revaccination*, when some degree of immunity is still present, never gives rise to microglia encephalitis but any discussion about the place of perivenous encephalitides will have to consider this fact.

*Group II F*

Five cases are grouped together, although their pathology is widely different The incubation time is mostly much shorter than in microglia encephalitis.

*Groups II G and H*

These groups need not be discussed in detail It is remarkable that in 7 out of 15 cases a well-known virus infection of the nervous system was activated: 6 cases of Heine-Medin's disease and one of herpes zoster. Bastiaanse considered his cases 3, 4, 8, 10 as post-revaccination encephalitis, but they showed the typical atrophic muscular paralyses of poliomyelitis, with serious sequelae. In 3 cases (Bastiaanse 2 and 12; Eckstein), an encephalopathic reaction must be taken into account.

*Case extracts* (only cases in which autopsy was performed are given)
*Group I B.*

*Case 42* Male, 26 years, known to have had diabetes for at least 5 years He had been vaccinated with good result against smallpox in early youth and was revaccinated 18. 5 1951. The pox pustules developed normally He fell ill on 20 5 with fever and general symptoms. Five days later coma came on Blood sugar 74 mg/100 ml With insuline the patient became mentally clear, but was in coma again on 27. 5 and died the same evening

Autopsy showed slight leptomeningitis and multiple small foci of polymorphonuclears, often with cocci in the centre, lying around a small blood vessel of the white or, more rarely, of the grey matter Around these foci we can sometimes find a zone of demyelination with glial reaction Diagnosis embolic encephalitis in a diabetic patient, following successful revaccination

*Case 18* (Bastiaanse 9, 1955) Male, 62 years Successful primary vaccination in youth, revaccination in 1901 and 16 8 1929, after which 3 small papules developed 23 8 mentally cloudy and drowsy, on the 28th somnolent, with nystagmus and positive Babinski and Kernig signs Increasing somnolence and death on 31.8 Wassermann reaction in the blood 4+ Autopsy showed the weight of the brain to be subnormal 1050 g At microscopic examination mild

perivascular lymphocytic infiltration was very diffusely present in the white *and grey matter; rarely* were abnormal cells seen in the parenchyma around these foci and no demyelination had taken place The condition of the ganglion cells was fairly good Larger foci did not exist Van Rijssel, who examined the case at autopsy, diagnosed it as an atypical general paralysis or syphilitic meningo-encephalitis, whereas Bastiaanse made a tentative diagnosis of encephalitis post revaccinalis.

*Case 43* Male, 58 years Revaccination 4. 5. 1951, with good skin reaction On 12. 5 he developed high fever, and he died the following day from heart failure. The brain showed senile changes, no inflammation. Due to the late autopsy, changes in the ganglion cells are of no value. But death was certainly not due to a cerebral disease Autopsy revealed acute myocarditis with scattered groups of polymorphonuclear leucocytes

*Case Sjövall 2*, 1932, is grouped here, although the result of the revaccination is not expressly noted but is presumably positive The patient died on the eleventh day, after an illness of 2 days. The inflammatory changes were limited to a perivascular adventitial reaction and oedema, with occasional glial reaction Venous thrombosis was also found Demyelination is not mentioned The clinical course was stormy, and the histological changes did not show microglia encephalitis The case could not be interpreted as a very early stage because death eleven days after vaccination is not too early for microglia encephalitis to be well developed (e g our case 9) This case of Sjövall must be classified as toxi-infectious encephalopathy

*Case Herckenrath*, 1935 (same as Eckstein, Sioli, Herzberg, 1932). Child, 3 years old. Primary vaccination when one year of age, without result. At 2 years she had a convulsion and at 3 years varicella. One month later revaccination was done (June 24th, 1931) On 30 6 vomiting occurred and she had another convulsion, after which hemiplegia was noted. Spinal fluid 10/3 cells, otherwise normal On the seventh day she had one more convulsion, then she developed a rash on the palms and soles. After several more convulsions the child recovered and two months after revaccination she was considered well, although with a slight defect of speech The child died a year later of an intercurrent disease Autopsy showed no abnormality of the brain which could be attributed to the previous encephalitis Some atrophy of cells in the cortex and basal ganglia is attributed by the author to another cause

The case is listed in this group because I cannot accept the diagnosis perivenous encephalitis here: the clinical course is quite different, short incubation time, very protracted course, frequent convulsions, lasting sequelae. A vascular encephalopathic reaction seems more plausible and the ganglion cell atrophy could well be attributed to that disease.

*Case Rammow*, 1935 Girl, 12 years of age, was vaccinated in her first year without result (no scars were found at autopsy) Revaccination with good result From the 7th day on she was ill, probably due to the vaccinia On the 12th day neurological symptoms developed, and death followed on the 18th day. Autopsy showed small-cell infiltration around vessels, punctate haemorrhages in the white matter, basal ganglia and lower structures This probably was a haemorrhagic encephalopathy, although the very short report cannot exclude microglia encephalitis with certainty.

*Case Döring 2*, 1942. Male, aged 27, is found dead 13 days after revaccination, without any preliminary symptoms Autopsy failed to show any serious changes in the organs, except oedema of the lungs. The brain showed the typical picture of encephalopathy· oedema, lymphocytic infiltration and slight diffuse proliferation of the glia

Doring believed this to be the earliest change of perivenous encephalitis and considered the case to have run a fulminating course Now we know that the fully developed picture of microglia encephalitis can be found at autopsy within 11 days of vaccination The lesions in Doring's case are more widely distributed and different in histological details (lymphocytes are not the important part in microglia encephalitis).

In a fulminating case of any disease, the lesions found at autopsy should be the first stage of what is also found in the more gradual development, but the picture in Doring's case is not a first stage of focal demyelination and microglial proliferation but the encephalopathic reaction of toxic- or post-infectious encephalitis The histological changes had probably existed for some time, and perhaps the patient had an epileptic fit or a heart attack during his sleep, which caused his death. H Jacob (1955), also regards Doring's case, as not belonging to the group of perivenous encephalitis.

*Case Anderson 9, 1942.* Male, 39 years, vaccinated in infancy and again on 4. 7 1942. Several days later found semi-comatous. No data about the duration of illness are given. Autopsy showed cerebral thrombosis.

*Group II F*

*Case 13* Male, 13 years old. Revaccination produced three small red papules, without vesicle formation. *Neurological symptoms developed on the 13th day.* Death occurred 2 days later. Autopsy showed signs of general septicaemic infection; the white matter of the brain was invaded by post-mortem bacterial growth. Encephalitis foci were present and consisted in some places of perivascular accumulations of polymorphonuclear cells with necrosis of the parenchyma. In other places a diffuse glial proliferation was found. In the mesencephalon perivascular foci with small, round cells occurred; plasma cells and some large lymphocytes and slight microglial proliferation in the parenchyma. Thrombosis of vessels was found in many places No perivascular demyelination could be found. Diagnosis: embolic septicaemic encephalitis following revaccination.

*Case 14.* Female, 13 years. The skin reaction to the revaccination was very mild; at autopsy (death occurred 9 days after vaccination) 4 scratches, covered with scabs, were seen The patient had epilepsy since childhood and was mentally backward. Six days after the revaccination she developed high fever with *soporous condition, low tonus of the extremities and continuous twitching of* the hands The spinal fluid came under normal pressure, with a normal protein value and cell count. Next day she had an epileptic fit, became somnolent and developed bronchitis. Death came on the 9th day after revaccination.

Autopsy showed marked hyperaemia and oedema of the brain, with many foci in the white matter, with perivascular lymphocyte cuffs, mixed with red blood corpuscles (Fig. 13). The foci were round, *not elongated along the vessels and often no connection with a vessel could be found* The parenchyma showed very slight microglial infiltration around the necrotic parts and a mild degree of demyelination, but many myelinated fibres were running through the focus In other parts of the brain similar foci can be found (Fig. 14), but the distribution is not typical for perivenous encephalitis *the brain stem is nearly exempt from* changes, the cerebellar white matter, however, contains many haemorrhagic foci.

This case is described by Querido (1930) as a typical case of post-vaccinial encephalitis, with very short incubation (6 days). As such,



*Fig 13. Haemorrhagic encephalitis* following revaccination. Pons; one large and three small haemorrhages; no glia proliferation. Case 14, cresylviolet



*Fig. 14. Haemorrhagic encephalitis* in myelin stain Case 14. Weigert Pal

it is often quoted in the literature. But Querido did not mention the *haemorrhagic character of many foci, the incomplete demyelination,* the shape of the foci (often round, not elongated), the abnormal localization of the lesions and the unimportant glial proliferation In our opinion, the case cannot be grouped with microglia encephalitis but is a haemorrhagic encephalitis, possibly belonging to Hurst's acute haemorrhagic leuco-encephalitis

*Case 15.* Male, 29 years Revaccination 26 9 1929 Three pustules developed within a few days On 3 10 he was mentally clouded. The C.S.F. was found to be normal Babinski sign positive Death came on 12 10 1929 Autopsy

showed healed gastric ulcer, with perigastritis, fatty degeneration of several organs; *pleuritis. The brain was markedly hyperaemic* and showed some haemorrhages around the lateral ventricles. There was oedema of the meninges. The subarachnoid space showed localized mononuclear infiltration. Many of the smaller vessels in the cortex and the white matter were thrombosed. Many vessels in the brain were accompanied by an increased number of oligoglial nuclei. Microglial increase was not seen. Around some vessels lymphocytes in small numbers could be found, but this was not of great importance.

*The most outstanding change in this brain was the myelin degeneration* especially in the white matter of the hemisphere, frontally more marked than elsewhere. In myelin-stained slides we saw small, round, white foci, 30—100 μ, sometimes appearing as empty spaces, sometimes containing a substance which still took the Weigert-Pal stain. There was no perivenous demyelination of the type seen in encephalitis following primary vaccination. A remarkable picture was seen also in the cortex, where numerous vessels showed *the same lipoid* masses found in the foci of the white matter, staining grey with the Weigert-Pal, in their Virchow-Robin spaces.

This substance was lying free and was not taken up by phagocytes. It was evidently being transported to the subarachnoidal space, where it can sometimes be found around the entrance or exit of penetrating vessels. This type of transport of myelin degeneration products was also found in the brains of three monkeys intraperitoneally injected by Verlinde *et al.* (1953, animals 145, 148, 165) with vaccinia virus and dead staphylococci. I have been unable to find any report on this curious type of myelin degeneration and transport in the literature.

*Case 56.* Male, 21 years old, vaccinated in youth, scars have not however, been observed. Revaccination 26 6 1957, gave a typical immune skin reaction, noted 1 7. Three days later he was forced to swim, but turned out to be slightly atactic. Afterwards he twice *fell from his bicycle*, complained of headache during the evening and was restless during the night. Early next morning he was found dead in bed. General autopsy showed serious vasomotor collapse, with haemorrhagic oedema of the lungs and oedema of the kidneys. The brain weighed 1500 g and was slightly swollen. At *microscopic examination, haemorrhages* were found around the lateral ventricles and in the cerebral white matter. Furthermore, diffuse perivascular *oedema of the brain was present.*

sometimes with a few small round cells and brown pigment included in phagocytes in the sheaths of some vessels

These changes were probably an early stage of a haemorrhagic encephalopathy, death being due to the pulmonary condition

*Case Baron 8*, 1929 Female, 28 years, developed angina on 29 1 1929, the next day injection of 40 ml antidiphtheria serum 1 2 revaccination, dried scabs of which were still present eight days later, without surrounding skin reaction On 5 2, serum exanthema developed, and soon disappeared again On 6 2 mild ataxia and progressive disturbance of speech were noted, and a soporous condition developed 3 days later Then the patient had several epileptic fits, and she died on 17 2 1929 Autopsy showed hyperaemia of the meninges and brain, with some haemorrhages, but without signs of encephalitis The vessels were filled with polynuclear leucocytes, indicating a general toxi-infectious condition No demyelination was found

In this case three aetiological factors were present. the sore throat, the anti-diphtheria injections and the vaccination. It is probable that the combination of these noxious conditions caused the vasomotor collapse, which is quite different from a perivenous encephalitis.

*Case Brouwer, de Jongh, Rochat*, 1933 In addition we will mention this case, in which revaccination may have played some rôle in the development of symptoms A motorcar driver, aged 27 years, was successfully vaccinated in his youth and revaccinated on 2 10 1929, showing immunity reaction On 31 10 he came into close contact with a patient with a haemorrhagic type of smallpox. He was then revaccinated on 5 11, again showing a very slight reaction A morbilliform exanthema was noted on 11 11, it was diagnosed as a very light case of smallpox His condition improved but on 21 11, signs of transverse myelitis developed, soon increasing to total paraplegia, causing death due to decubitus on 27 1 1930

Pathological examination showed large myelitic foci with necrosis, marked demyelination, fatty granule cells, microglial syncytia and fibrillar glial sclerosis Small round cells were present in the subarachnoidal space, but were rarely found around parenchyma vessels The ganglion cells were mainly intact Very few small foci were found in the oblongata and the pons, the cerebellum and cerebrum showed no changes

The authors conclude that the lesions are typical of myelitis following smallpox. Whether the partial immunity and the revaccinations had

any influence on the eruption, or development of the myelitis, cannot be decided at present.

*Discussion*

The number of cases with an accurate histological description is too small for statistical evaluation, but still some general conclusions may be drawn.

(1) In the first place it is evident that *microglia encephalitis is not the prevailing nervous complication following revaccination*. In our group D, several cases may have been microglia encephalitis but, as they recovered, their exact nature cannot be given. At least 4 of these did not recover completely, but still showed neurological defects after some time. Most probably they do not belong to the microglial group.

(2) The most outstanding conclusion, however, is that microglia encephalitis has not been observed following revaccination when partial immunity to the vaccine still existed but that, when immunity had subsided, the cerebral reaction might be the same as that following primary vaccination. However, the picture may be rather irregular, as described by Pette (1936, p. 271) in a girl, aged 12 years, in whom resemblance to the picture of disseminated encephalomeylitis existed (no data about the skin reaction or incubation time are given by the author). Then, the proportion of cases with cerebral reactions other than microglia encephalitis is much larger than we are accustomed to see following primary vaccination.

(3) Clinically the wide variation in incubation period as well as the irregular course of the disease and the great number of cases recovering with neurological sequelae, are outstanding differences from the picture of microglia encephalitis seen after successful vaccination.

(4) Then, we found that activation of another virus disease is seen after revaccination as well as following primary vaccination (Heine-Medin, zoster, myocarditis)

(5) The number of cases in this section is too small to discuss the problem of the possible influence of cerebral complications when other serum injections or vaccinations had been given in the same period

(6) As far as we know, there is only one report on revaccination of persons who had encephalitis following a primary vaccination. Puntigam and Daimler (1950) report on 11 soldiers; none of them showed any nervous reaction following revaccination

(7) Nervous reactions following revaccination have been known for a long time. In 1916 an accumulation of cases of brachial neuralgia was seen by many physicians during an intensive vaccination campaign in the Netherlands (400,000 revaccinations). Thoracic neuralgia also occurred and the clinical picture somewhat resembled Bornholm's disease but there were no relapses after recovery and the pains were not as severe as those in the latter disease. The incubation time was about 14 days. This complication was also noted in 1929 (Koetser, 1929) and again only following revaccination. Women were more frequently affected than men

### d. Development of another disease during the first weeks following vaccination

In this paragraph some cases will be discussed in which a well-known nervous disease started shortly after vaccination, suggesting some relation between its occurrence and the vaccine treatment.

*No 21* 7 Months old, developed cerebral symptoms 20 days after vaccination She died many months later of pyaemia and septic meningoencephalitis.

*No 42.* Man, 26 years Revaccination, died 8 days later of embolic encephalitis (see par. c)

*No 46* 14 Months old, developed meningococcal meningitis 8 days after vaccination, which ran a fatal course in 6 months.

Then our attention should be drawn to cases of *poliomyelitis* starting after vaccination Our series shows only one case (No 23) in which the paralysis developed on the 14th day; the child died one week later The histological picture was typical in her case and also in the nervous system of a monkey injected with material from this patient

The histological and experimental evidence in this case proves that, here at least, the vaccination may have been a factor which made the outbreak of the Heine-Medin infection possible. For this case we cannot accept the explanation which van Bogaert (1956) gives: that a former subclinical or mild poliomyelitis infection leaves a segment of the spinal cord more vulnerable, after which vaccination may cause symptoms reminiscent of recurrence of the poliomyelitis.

The Dutch literature contains a number of articles on this subject, the results of which are summed up in Table VII

TABLE VII

CASES OF POLIOMYELITIS FOLLOWING VACCINATION

From the Dutch literature

| *Author* | *Year* | *Age of patient* | *Incubation days* | |
|---|---|---|---|---|
| Burgerhout | 1929 | no data | given | Clinical observation only. |
| Bastiaanse | 1929 | 6 y | 17 | Revaccin Atrophy of muscles and paralyses remained |
| Bastiaanse | 1929 | 10 y. | 20 | Revaccin. On 20th day convulsions, hemiplegia. |
| Bastiaanse | 1929 | 30 y. | 10 | Revaccin. On 15th day pareses: remaining atrophy. |
| Bastiaanse | 1929 | 7 y. | 7 | Revaccin. Flaccid paralyses; remaining atrophy. |
| de Monchy | 1930 | 27 mo | ca 10 | Paralysis of arm on which vaccin. took place |
| Heidema | 1930 | 2½ y | 9 | Paraplegia. More cases of polio in the town. |
| Bakker | 1930 | 30 y. | 10 | First hemiplegia; later also paraplegia |
| v Rijssel | 1930 | 16 y | 14 | Hemiplegia. Histological confirmation |
| No 23 | 1940 | 9 mo | 14 | Histological confirmation |
| Verjaal | 1947 | 21 mo. | 14 | Clinical observation |
| Verjaal | 1950 | 10 mo | 21 | Clinical observation |
| Verjaal | 1950 | 3½y. | 21 | Revaccin Transverse myelitis No proof of Heine Medin |

In other countries also, a number of cases were described in which poliomyelitis developed shortly after vaccination. Some relation between the two is generally accepted. Miller (1953) reports on 3 cases. Uiberall (1950), however, did not find an increase in poliomyelitis incidence following mass vaccination.

Our material contains two cases (Nos. 43 and 55), in which death from acute (probably viral) *myocarditis* occurred on the 9th and 10th days after successful vaccination, respectively.

A discussion of this subject cannot be given here, as our work is mainly based on the cases with histological examination, and these are only a small minority, which does not permit of any conclusions.

The extensive literature on this subject need not be discussed here. However, mention should be made of administration of *cortisone* before experimental or accidental viral or other infection. Wolf *et al.* (1952) found that monkeys, carrying *Trypanosoma cruzi* and injected, after cortisone treatment, with monkey brain and adjuvants, developed trypanosomal encephalitis, whereas animals treated in the same way but with no previous administration of cortisone, dit not show this disease.

Then, monkeys that received intracerebral injection of Echo 9 virus at the same time with cutaneous vaccination (smallpox vaccine), did not show any sign of encephalitis unless they had previously received cortisone treatment, in which case encephalomyelitis of the poliomyelitis type developed (Verlinde, 1955)

*A case*, recently described by *Paul* (1954), perhaps belongs in this paragraph. A child, 13 months old, had a severe convulsion 8 days after vaccination, and remained a spastic imbecile The mother and the child showed a positive Sabin test for toxoplasmosis, and Paul gives as an explanation that the toxoplasmosis was an important factor in the development of postvaccinial encephalitis

But we think perivenous encephalitis never existed in this case. Perhaps it was the other way round, vaccination activating toxoplasma growth, perhaps it was a common toxi-infectious vascular reaction

**e. The encephalopathic brain reaction following vaccination**

We have examined 22 cases in which death followed vaccination within 4 weeks, with a pathological picture showing the changes generally grouped together as encephalopathic. Many of these cases have already been discussed in the preceding paragraphs in another connection.

They can be divided into 3 groups (see Table VIII): I. those, in which clinically no encephalitis was noted; II. cases showing a convulsion without (other) signs of encephalitis, and III. cases with clinical symptoms of a brain affection, often called encephalitis.

The most frequent, and probably the most important, is *oedema of the brain* manifested by increased weight, swelling of the convolutions and widened perivascular spaces (see Table VIII). Sometimes the pericellular spaces were also larger than usual. Oedema was found in all cases of group II, starting with a convulsion and in most cases of group I, but only in one of 3 cases in group III. In the last group, however, comprising cases with symptoms pointing to an affection of the brain, changes such as hyperaemia, slight cellular infiltration and early glial reaction were more constant than in groups I and II. The reaction of the brain parenchyma and its vascular apparatus is definitely more marked in the third group than in the first two groups, although the duration of the illness has also been very short in three of them.

The *infiltration of the meninges* and sometimes of the vessel sheaths was never very important; generally only a few cells were found in the tissue covering the cerebral sulci or in the cisternae. They consisted of small lymphocytes with rare large lymphocytes or plasma cells. Polynuclears were not important and the distribution in the meninges was not perivascular In the vessel sheaths in the brain, cellular infiltration was never very evident, a few lymphocytes were found only in some cases.

The *degeneration of ganglion cells* was quite conspicuous in a number of our cases but in very young children, and in the presence of cerebral oedema, the swelling and vacuolization of the cortical cells can easily be due to post-mortem changes (or even to swelling during the

TABLE VIII

POSTVACCINIAL ENCEPHALOPATHIC REACTION

Dutch autopsy cases

| Case No | Age | Incubation, days | Prim or revacc. | Survival after vaccination | | Pia hyperaemia | Pia infiltration | Parenchymal hyperaemia | Oedema, general or perivascular | Perivascular cells | Haemorrhages | Degeneration of ganglion cells | Glia reaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *I Death without clinical cerebral involvement* | | | | | | | | | | | | | |
| 58 | 4 mo | 0 | P+ | 13 | convulsion 5 w before death shock, exsiccated. | — | + | + | 675 g | — | — | oedema | — |
| 20 | 6 mo. | 2 | | 3 | ½ day ill Morbilli exanth at autopsy. No cause of death. | — | + | ± | | ± | + | ++ | + |
| 49 | 7 mo | 7 | | 7 | Found dead in bed. No preceding disease Body autopsy neg. | ± | — | + | 880g | — | — | — | — |
| 22 | 8 mo | 5 | | 6 | Malaise 1 day. Then dead in bed Thymus pos | + | ± | ± | | — | — | + | oligo+ |
| 50 | 9 mo. | 2 | | 2½ | Malaise, circulat. collapse. Shock Thymus pos. | — | ± | — | 1100 g | ± | — | ++ | — |
| 4 | 10 mo. | | | ±8 | Chron eczema Vaccinia gener Sister vaccinated | — | — | + | | ± | — | ++ | + |

| *Case No* | *Age* | *Incubation, days* | *Prim or revacc* | *Survival after vaccination* | | *Pia hyperaemia* | *Pia infiltration* | *Parenchymal hyperaemia* | *Oedema, general or perivascular* | *Perivascular cells* | *Haemorrhages* | *Degeneration of ganglion cells* | *Glia reaction* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 47 | 11 mo. | 8 | | 9 | 1 day fever. Dead in bed. Body organs neg. | ± | ± | — | — | ± | — | — | oligo + |
| 59 | 14 mo | 5 | P + | 5 | Evening fever. Morning dead in bed Thorax purpura. | ± | ± | — | 1150 g | — | — | — | ± |
| 60 | 18 mo | 18 | | 18 | Vaccinia gener. Fulminant death | — | + | — | + | — | thrombi | ± | oligo ± |
| 55 | 20 y | 10 | P | 10 | Found dead in bed. No disease. Autopsy myocarditis | + | + | | 1600 g | ± | — | ++ | — |
| 43 | 56 y | 8 | R + | 9 | Fever. Mors subita. Autopsy myocarditis | + | — | — | — | — | — | + | — |
| 61 | 7 mo. | 12 | P + | 12 | No disease. Dead in bed Spleen infectious cond. | — | ± | — | — | — | — | — | — |
| 62 | 6 mo. | 5 | | 5 | Found dead in bed. Autopsy malformation of cerebellum | — | ± | — | + | ± | + | | — |
| II | *Death after convulsions, without other clinical cerebral disease* | | | | | | | | | | | | |
| 54 | 7 mo | 9 | P + | 10 | Normal until convulsion. Subarachnoid haemorr. | — | ± | — | 950 g | — | — | + | — |
| 34 | 8 mo. | 5 | | 9 | Status epilepticus | + | — | ± | | — | — | oligo + | ± |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 51 | 9 mo | 8 | | 8½ | Had cold No disease before convul Blood 24000 leucoc S F. 8 cells Thymus + | — | — | — | 1000 g | + | — | — | — |
| 26 | 10 mo | 6 | | 7 | 5th day fever At night convul. | — | + | + | | + | — | — | ± |
| 57 | 11 mo | 24 | | 24 | Fever, convulsions. Death after few hours Poliovirus in pons | — | ± | — | peri-vasc | ± | ± | ± | — |
| 52 | 24 mo | 10 | | 70 | Fever before convulsion. Later deep idiot Vascul. malacia of brain. | No inflammation found, brain weighed 1150 g | | | | | | | |
| II | *Cerebral disease and histological encephalopathy* | | | | | | | | | | | | |
| 36 | 9 mo | 3 | | 8 | Progressive illness. Toxic, diarrhoea, restless. | + | | + | | + | | ± | |
| 48 | 16 mo | 10 | P + | 11 | Father flu Pockpustules 9th day Illness 8 hours | + | + + | + + | peri-vasc. | — | — | + | glia-star |
| 35 | 5½ y | 6 | P | 6 | Mother rubella during pregn. Malaise, convuls 6 hours later death | + | + | + | — | — | — | | oligo + |
| 56 | 21 y | 7 | R— | 7½ | One day headache Dead in bed vasomotor collapse Haemorrh pneumon Old brain lesions | — | + | | 1500 g | ± | + | old | — |

first weeks of fixation in formalin solution) and should not be mistaken for a toxic effect on these cells.

*Demyelination* was never found in these cases and the reaction of the glia cells was very moderate, mostly consisting of some increase in the number of oligoglial nuclei, often arranged in rows along small vessels or in the direction of the nerve fibres.

*Four cases in which death could definitely be ascribed to a disease* other than cerebral changes (group I, Nos. 4, 43, 55, 60) give the same histopathological picture as the others. Two of these died of vaccinia generalisata and two of myocarditis. The general toxic and infectious condition of these patients, therefore, was reflected in their nervous system by the same changes as found in the others

A further interesting point is that *no difference can be found between the early and the late cases.* No. 20 had no aetiology other than vaccination and an enlarged thymus, and still the changes are of the same character and grade as in the others Therefore these changes cannot be seen as *the initial stage of another disease (microglia encephalitis), as supposed* by some authors, but they constitute a disease as such, giving the complete picture of the encephalopathic brain reaction to toxi-infectious conditions of the body. The question as to whether we should speak of infectious changes or of post- or para-infectious conditions seems to me an academic one, of only little importance for an understanding of the pathogenesis There is no sharp borderline between the two; even in a very mild general disease, the vasculo-connective tissue of the brain shows some changes; but these subside as soon as the general disease improves. Only those cases in which the brain symptoms and *histological changes do not disappear after* improvement of the general condition, should be called post- or para-infectious, and considered complications

*Our table shows one more interesting aspect · there is no clear difference between the groups without and those with convulsions.* The convulsion is mostly preceded by a short period of fever and malaise, which can be considered an expression of the developing oedema of the brain. This *oedema was found in all cases of group II on which sufficient data* were available. In case 57 the vaccination, done 24 days prior to the

fatal outcome, cannot have been of much importance, but the findings of virus of poliomyelitis in the brain must probably lead us to the explanation that the viraemia caused a toxi-infectious condition resulting in brain oedema and a convulsion. Whether the vaccination acted as an accessory factor remains open to discussion, it is certainly possible.

*Case 52*, surviving the convulsion for 2 months, of course shows another histological picture because the serious damage caused by the anoxaemia during the convulsive state (lasting about 2 hours) was evident at death. In the other cases, however, death came on too quickly for changes due to the convulsion to be demonstrable. Radermecker (1958) makes a very careful analysis of convulsions during hyperthermia and also considers them to be non-specific cerebral reactions to general infectious processes

The great number of patients who were *found dead* without important *preceding symptoms being observed by their surroundings, is astonishing* We encountered this 6 times in small babies and twice in adults (No 55, a soldier with myocarditis; No. 56 found dead at night after he had complained of headache during the evening). Miller, 1953, also points out this sudden death, 3 of his patients (all soldiers on active service) died within 24 hours after the first symptoms. It is very likely that at least 2 of them, dying 2 and 5 days after vaccination, had an encephalopathy rather than perivenous encephalitis Doring also describes a man of 27 years, found dead 13 days after revaccination, with encephalopathic changes in the brain (this case has been discussed in the paragraph on revaccination).

We must consider the brain oedema in these fulminant cases, together with circulatory collapse, to be the chief cause of this spectacular course

The fact that small babies formed the majority of our cases of encephalopathy is not astonishing when we realize that the cause of death is often general shock, and that the brain oedema noted in most of these cases more easily develops in the very young brain than in the older brain Several cases had an enlarged thymus, predisposing them to circulatory disturbances

The *encephalopathic changes* discussed in this paragraph, of course, are not specific for postvaccinial disease, but are a very common reaction of the nervous system to many toxi-infectious conditions. It is not necessary to describe these in detail but it might be worth mentioning that the same changes of the brain can be found in patients in whom a nervous disease was not clinically present and who did not even show any nervous symptoms. This is important in our discussion, because we can more easily accept that the mild cerebral changes found in a number of cases after vaccination are an expression of the condition of vaccinia and the general disease following vaccination, and not a complicating brain disease. The difference in incubation time (as shown in Fig. 15) between these cases and those of microglia encephalitis, stresses this point further.

Age in years

| Age in years | Number of cases |
|---|---|
| 0 | 14 |
| 1 | 4 |
| 2 | |
| 3 | |
| 4 | |
| 5 | 1 |
| 6 | |
| 7 | |
| 8 | |
| 9 | |
| 10 | |
| 11 | |
| 12 | |
| 13 | |
| 14 | |
| 15 | |
| 16 | |
| 17 | |
| 18 | |
| 19 | |
| 20 | 1 |
| 21 | 1 |
| 22 | |
| 23 | |
| 24 | |
| 36 | 1 |

Incubation in days

| Days | Number |
|---|---|
| 0 | 1 |
| 1 | – |
| 2 | 2 |
| 3 | 1 |
| 4 | – |
| 5 | 3 |
| 6 | 2 |
| 7 | 2 |
| 8 | 3 |
| 9 | 1 |
| 10 | 2 |
| 11 | – |
| 12 | 1 |
| 13 | – |
| 14 | – |
| 15 | – |
| 16 | – |
| 17 | – |
| 18 | 1 |
| 19 | – |
| 20 | – |
| 21 | – |
| 22 | – |
| 23 | – |
| 24 | 1 |

Survival in days

| Days | Number |
|---|---|
| 0 | |
| 1 | |
| 2 | 1 |
| 3 | 1 |
| 4 | |
| 5 | 1 |
| 6 | 2 |
| 7 | 2 |
| 8 | 3 |
| 9 | 3 |
| 10 | 2 |
| 11 | 1 |
| 12 | 1 |
| 13 | 1 |
| 14 | |
| 15 | |
| 16 | |
| 17 | |
| 18 | 1 |
| 19 | |
| 20 | |
| 21 | |
| 22 | |
| 23 | |
| 24 | 1 |
| 75 | 1 |

Fig. 15 Dutch cases of postvaccinial encephalopathy that came to autopsy.

We shall describe one case belonging to this category *No 5259*, a child of *11 months, fell acutely ill with abdominal pain* for which an operation was done The disease, however, was progressive and the child died about 5 days after the first complaints, without having shown nervous symptoms Routine examination of the brain, however, showed very marked oedema: *the brain* weight was 1120 g. and, microscopically, perivascular oedema was also found.

as well as spongious oedema of the cortex, sometimes with laminar distribution. Another change was diffuse hypertrophy of the walls of small vessels in the parenchyma. Cellular exudate was not important. A lead or arsenic poisoning was considered but could not be proved. *Summarizing, important histological changes in the brain were found in a young child with abdominal disease, without any clinical symptoms.*

The literature contains many articles pointing out this important fact. Pagès (1952) divides the pathological changes in toxicoses of babies into 3 groups: hyperaemia, sometimes with thromboses and haemorrhages; then, oedema of the brain and meninges and, thirdly, ganglion cell degeneration. Annell (1953), in an article on pertussis in infancy, mentions that a psychopathy in later childhood can very often be caused by encephalopathic changes during the pertussis, which did not impress as important neurological symptoms at the time. She also mentions that these complications have increased in frequency in the third decade of this century.

That cerebral changes can be present without clinical symptoms is also demonstrated by Hodes and Livingstone (cited by Radermecker, 1956). They found that, out of 114 cases of measles without cerebral symptoms, 43 showed E.E.G. changes suggesting subclinical "encephalitis".

## f. Rare histological pictures

Some cases showed a microscopic picture that could not be classified or brought under the well-known headings. All occurred after revaccination; descriptions of these cases are given in par. c, (cases 13, 14, 15, 18). Bastiaanse put them together as revaccination encephalitis, but in our opinion they show too many differences, among each other and from other cases occurring after revaccination, to unite them in one group. The greater complexity of the microscopic picture suggests a more complicated aetiology, in which the earlier primary vaccination probably plays an important rôle.

*Chapter 5*

# OCCURRENCE OF MICROGLIA ENCEPHALITIS AND MICROGLIAL PERIVENOUS REACTION BEFORE *1923*, AND WITHOUT PRECEDING EXANTHEMATOUS DISEASE

**a. Introduction**

In this chapter we shall review the occurrence of perivascular microglial proliferation in conditions other than those so far described. Many cases have been described in the literature as perivenous encephalitis or disseminated encephalomyelitis, often giving to these conceptions a rather broad pathological basis. It will be our aim in *this chapter to divide these cases into a group, limited strictly to the* picture of microglia encephalitis (+) as opposed to a less homogeneous group comprising cases differing from these in some points but all showing perivenous microglial proliferation and demyelination (±) and others with the characteristics of another reaction (-). We presume that only by narrowing down our group in this way will it be possible in the future to relate a certain pathology to definite aetiological factors. A discussion of the results obtained will be postponed until the next chapter.

*Microglial proliferation* occurs in many diseases, and we need not describe these. Only when focal perivascular infiltration is seen with this type of cells can the pictures resemble those of microglia encephalitis. Some figures will illustrate this. Fig. *11, (p. 70)* shows the lateral



Fig 16a Fat embolism, microglia reaction around necrotic centre, not spreading along the vessel Case 5336, death 7 days after trauma Nissl stain.

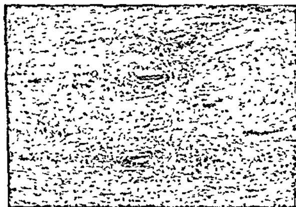


Fig 16b. To compare with a microglia encephalitis Focus along normal vessel Case 45 Nissl stain

ganglion cell degeneration with neuronophagy is apparent (not shown in the figure), and thick lymphocyte cuffs are present around many vessels without a microglial reaction. Demyelination is scarce or absent. Some degree of marginal gliosis may be present (case 23; girl 9 months old; illness began 15 days after vaccination; three days later paralyses developed and, again 3 days later, a fatal outcome. Inoculation of spinal cord tissue into a monkey was positive for Heine-Medin virus).

This microglial proliferation occurs in many different diseases of the C.N.S., and can easily be distinguished from the postvaccinial foci. Also, its distribution along the cerebral axis is quite different.

*Perivascular foci* occur in a variety of diseases. Embolic encephalitis shows pictures, in which the glial proliferation is more often perivascular (Fig. 16 a, case of fat embolism, No. 3620, death 7 days after trauma), but necrosis in the centre is generally present and the focus is arranged also around very small vessels, not only the larger veins. Demyelination is often incomplete. Often there is some haemorrhage in the foci (compare with 16 b, a typical focus of microglia encephalitis).

In many toxi-infectious conditions foci can be found which resemble this type. Generally oedema and changes of the vessel wall indicate their true nature, and they will not be mistaken for microglial foci.

In *haemorrhagic encephalopathy* we previously described (Chapter 3, b, 4) foci of partial tissue necrosis of vascular origin, and the subsequent microglial reaction. These foci differ from microglia encephalitis in that they are more rounded, much smaller (not infiltrating far into the parenchyma), showing only incomplete demyelination. Thrombosis of the vessel or thickening of its wall is often present. In addition, the distribution of the foci can be different. In these cases we do not find marginal gliosis and rarely more diffuse glial proliferation.

Differential diagnosis is far more difficult in cases where, *in addition to the changes typical of the disease, perivenous foci of demyelination with microglial proliferation occur.*

In the first place we must mention some rare cases of *poliomyelitis*, in which typical microglial foci were observed. G. Peters (1938) and Mollaret and Bertrand (1951) demonstrated these in the white matter of the cord and hemispheres. We observed a similar picture in two monkeys which had received an intracerebral injection of Echo 9 virus at the same time with cutaneous anti-smallpox vaccination (Fig. 17).



FIG 17. Perivenous microglia proliferation in clinical poliomyelitis Monkey, injected with Echo virus Thalamus Nissl stain

Both animals developed paralyses and autopsy showed the typical lesions of acute anterior poliomyelitis in the spinal cord, but also more involvement of the higher centres, especially the thalamus In these centres several typical perivenous foci of demyelination with microglial and polynuclear proliferation occurred, but the foci showed

marked hypertrophy of the vascular walls and also infiltration by mesenchymal cells.

Perivenous foci have been described in cases which also showed other types of lesions; they will be reviewed in the following paragraphs. In par. f, a short discussion is given on disseminated encephalomyelitis, to which group many of these cases belong.

We will regard as *positive signs of microglia encephalitis*:

Perivenous microglial proliferation;
Marked demyelination in these areas;
Less degeneration of the axis cylinders;
Marginal gliosis by microglia cells;
Small or no lymphocyte cuffs;
Diffuse but not very severe glial proliferation in white and grey matter;
Distribution in hemispheral white matter, in white and grey matter in the deeper structures;
Sparing of ganglion cells in the foci.

And we regard as *negative signs*:

No necrotic centre in the foci;
No or only agonal erythrocytic infiltration;
No thromboses of vessels;
No coalescence to foci in which the original perivascular localization is not evident.

The occurrence of these changes would point to another reaction type, probably to a complicating aetiological factor.

Table IX summarizes the cases with autopsy reports referred to in the literature as perivenous encephalitis, with the exception of post-vaccinial and post-measles cases (they are very numerous); not all post-rubella cases are included

**b. Cases occurring before 1923**

The case reported by Brissaud and Brécy, in 1904, as „neuromyélite optique", had multiple lesions with lymphocyte exudates, but no cells in the parenchyma (according to the figures); there were some haemorrhagic foci but it does not resemble microglia encephalitis. It is referred to by some authors as a case of perivenous encephalomyelitis.

TABLE IX

AUTOPSY CASES REFERRED TO AS PERIVENOUS ENCEPHALITIS IN THE LITERATURE

(Shortly mentioned in the text)

| *Author* | *Year* | *Rating* | *Aetiology* |
|---|---|---|---|
| Peters | 1938 | ± | poliomyelitis |
| Mollaret, Bertrand | 1951 | ± | poliomyelitis |
| Brissaud, Brécy | 1904 | — | |
| Turnbull, McIntosh | 1912 | ± | vaccinia |
| Krabbe | 1913 | ± | |
| Marie, Tretjakoff | 1921 | + | feverish disease |
| Tinel, Bénard | 1921 | + | rubella |
| Wohlwill | 1928 | + | no known etiology |
| Pette, 2 | 1928 | ± | |
| Grinker, Bassoe, 1 | 1931 | — | common cold |
| Müller | 1923 | ± | |
| De Busscher, Radermecker | 1949 | + | vaccinia 28 d. earlier |
| Van Bogaert, 2 | 1950 | ±? | |
| Briggs | 1935 | — | rubella |
| Wigand | 1941 | — | rubella |
| Moller, 117 | 1949 | + | rubella |
| Falger | 1943 | +? | rubella |
| Zimmerman-Yannet | 1931 | — | varicella |
| Van Bogaert | 1930 | — | varicella |
| Roeder-Kutsch | 1944 | + | varicella |
| Dagnelie, Dubois | 1932 | — | varicella |
| Swan | 1946 | — | varicella + angina |
| Spiller | 1903 | — | smallpox |
| McIntosh, Scarff | 1930 | — | smallpox |
| Kramer, 7 | 1951 | — | smallpox |
| Kramer, 8 | 1951 | — | smallpox |
| Troup, Hurst | 1930 | ± | smallpox |
| Marsden, Hurst, 1 | 1932 | + | alastrim |
| Marsden, Hurst, 6 | 1932 | + | alastrim |
| Marsden, Hurst, 7 | 1932 | + | alastrim |
| Brouwer, de Jong, Rochat | 1933 | + | mild smallpox |

| Author | Year | Rating | Aetiology |
|---|---|---|---|
| Schreuder, van Rijssel, Verlinde | 1950 | + | cowpox |
| Winkelman | 1942 | — | scarlet fever |
| Moller, 92 | 1949 | — | Whooping cough |
| Donohue | 1941 | + | parotitis |
| Greenfield | 1930 | + | influenza |
| Greenfield | 1930 | +? | influenza |
| Demme | 1930 | ? | angina |
| Davison, Brock, 1 | 1937 | —? | common cold |
| Davison, Brock, 2 | 1937 | — | common cold |
| Moller, 2 | 1949 | +? | common cold |
| Crome | 1954 | — | influenza |
| Higier | 1912 | ± | rabies + anti-treatment |
| Rojas | 1932 | ± | rabies + treatment |
| Bassoe, Grinker | 1930 | +? or ± | rabies-treatment |
| Stuart, Krikorian | 1930 | — | rabies-treatment |
| Uchimura, Shiraki | 1957 | — | rabies-treatment |
| Jones | 1958 | — | rabies-treatment |
| Griffin, Rogers, Kernohan | 1948 | — | antityphoid inj. |
| Giedeon | 1954 | — | antityphoid inj |
| De Massary, Albeissar | 1936 | — | subacute course |

*1. Turnbull and McIntosh* (1926) described a case occuring in 1912. A boy, 15 years old, was vaccinated 5. 7.1912. No scars from previous vaccination were present, and the skin reaction took the course of a primary vaccination. On the 18th he became comatous, oculomotor palsy was noted the following day. On 22. 7 the C.S.F. contained numerous cells one third being polymorphonuclears. He died from mucopurulent bronchopneumonia on 22. 7. Autopsy showed degeneration of the kidneys and calcified mesenteric glands. The brain weighed 1148 g. Subdurally and in the subarachnoid space, small haemorrhages were found. One cortical block and 5 levels of the spinal cord were histologically examined. The cortex showed hyperaemia, with lymphocytes and erythrocytes around a number of vessels. Very little glial proliferation either in grey or white matter and no demyelination, other than what could be attributed to perivascular oedema.

In the spinal cord, at all levels, foci of demyelination were found perivascularly, with the typical longitudinal arrangement. However, microglial proliferation in these areas is very mild, as also stated by Turnbull. The foci are localized mainly in the white matter; in some of them haemorrhage was present (thor. VI) and oedema was conspicuous in all

Turnbull mentions that the demyelination is more easily seen with the van Gieson stain than in Weigert-Pal-stained slides, which might mean that oedema was more important than primary myelin loss. The picture evidently differs from microglia encephalitis in many points, but still the spinal foci show enough similarity with it to be of importance for a final explanation.

2. *Krabbe* (1913) published the case of a one-year-old child, who died 12 days after the onset of disease, which started with diarrhoea After 5 days he was restless, he developed diplopia two days later and had some rigidity of the neck. Symptoms changed in the course of the disease and he had convulsions and tonic rigidity The spinal fluid showed high pressure and a mild increase of mononuclear cells The brain showed hyperaemia, no meningitis. Microscopically the most interesting change was a focal perivascular increase in glia cells, with distinct plasma bodies The photograph seems to confirm that a perivenous microglial focus is demonstrated here. There were no mononuclear or other haematogenous cells The distribution of these foci was mainly subcortical and deeper in the white matter Demyelination in the foci was typically perivascular In addition a few granule cells, laden with fat, were found in vessel sheaths and also there existed a mild, very diffuse increase in small round glial nuclei. Krabbe considers this case to be a very early stage of diffuse familial sclerosis, and not an inflammatory condition The child had not been vaccinated, nothing is known about previous diseases*. A brother had a similar condition at the age of 2 years, but recovered.

3 *Marie and Tretjakoff* (1921) described a girl, 16 years old, falling ill on 30 11 1918, with fever and eye muscle paralysis. A week later paraesthesia and weakness of the legs developed and the disease ran an ascending course, with death on 17 12 Nothing is noted about previous vaccination, no aetiology could be found Autopsy revealed inflammatory lesions, limited to the white matter of the cord, brain stem and centrum semiovale The lesions consisted

* Personal communication

of foci of demyelination arranged perivascularly, oval or rather long in shape. They contained granule cells and glia cells. The ganglion cells were found to be intact.

The authors do not discuss the pathology; to them it is one of the types of changes found in Landry's ascending paralysis, but the figures are very suggestive of perivenous microglia encephalitis

4. *Tinel and Bénard* (1923) briefly refer to a case of post rubella encephalitis, occurring in a man aged 21, in 1921. Death occurred on the 6th day after eruption of the exanthema, 2 days after the first neurological symptoms had appeared. In the spinal cord (other parts could not be examined) numerous small perivascular foci existed with total demyelination and cellular infiltration by mononuclear cells (called plasma cells) in the vessel sheaths and surrounding tissue. All nerve cells were perfectly well preserved. The spinal fluid had shown infiltration, mainly by polynuclear leucocytes

The figures given by Tinel and Bénard show a great resemblance to perivenous encephalitis; the spinal fluid reaction, however, and absence of glia cell proliferation, could indicate that embolic encephalitis cannot be excluded

These cases show some points of resemblance with our picture of microglia encephalitis; however, only the cases by Tinel and Bénard, and by Marie and Tretjakoff can be accepted as probably true microglia encephalitis.

**c. Cases without preceding disease**

This paragraph contains cases, sometimes typical sometimes not quite so but with enough points of resemblance to be taken up in our discussion

*Case of Krabbe* (1913), discussed above

*Case of Marie and Tretjakoff* (1921), discussed above.

*Case of Wohlwill* (1928). In a very short discussion Wohlwill mentions this case with the picture of perivenous encephalitis, but he does not give enough details for its final establishment in a certain group.

*Pette, case 2*, 1928 One microphotograph of this case very much resembles perivenous microglial proliferation. The other pictures

indicate another type of encephalitis, and the case is diagnosed by Pette as disseminated encephalomyelitis or acute multiple sclerosis.

*Grinker and Bassoe, case 1*, 1931. Female, 23 years; 10 days after contracting a cold, nervous symptoms and fever set in, of which she died 6 days later. The symptomatology was that of myelitis, with mental cloudiness. Death from bronchopneumonia. Leptomeninges and sacral roots were infiltrated by white blood corpuscles and fatty granule cells. Necroses in cord, often around veins, coalescing and with many granule cells. Demyelination was marked. Hemispheres were not involved The case has, according to Grinker and Bassoe, the same pathology as Greenfield's cases following influenza and postvaccinial or post-measles encephalitis Still, according to us, there is a marked difference After 5 days of illness, microglia encephalitis does not show total necrosis with many fatty granule cells, and the perivascular and meningeal reactions are much less. It is comparable to our cases of transverse myelitis, in which secondary factors alter the picture. But it is not certain that a typical microglia encephalitis was the original disease

*Muller* (1933) This case shows typical microglia encephalitis in the white matter of the cerebral hemispheres, but also shows many haemorrhagic foci, with vascular thromboses and necrotic centre. Both types of foci show demyelination No meningeal affection; no marginal glial proliferation and rather marked astrocyte proliferation in the foci are other points of difference with microglia encephalitis

*Van Hasselt* (1934). We mention this case, because it is sometimes quoted in the literature, although the description suggests an embolic or haemorrhagic type of encephalitis We cannot include this case in the microglia encephalitis group

*De Busscher and Radermecker* (1949). This case has been reviewed in Chapter 3 b, 5 (myelitis) It showed typical microglia encephalitis, starting 28 days after successful smallpox vaccination, together with typhoid vaccination As has been suggested by the authors, it seems more accurate to group it with the cases without known aetiology than with postvaccinial encephalitis

*Van Bogaert, case 2*, 1950. Girl, 9 years old, had measles 3 years before with cerebral symptoms, but recovered. Fell ill 14 days before death, with general symptoms, after which cerebral symptoms developed. Transverse myelitis with beginning decubitus. No infectious condition had been noted before the illness started. Perivascular infiltrates in demyelinated areas were found throughout the white matter of the hemispheres. No specification of the type of cells or of the appearance of the lesions in other than myelin-stained sections is given, but the case is classified by van *Bogaert* as post-infectious encephalomyelitis, activated by some general infection and showing the same type as the child had shown 3 years earlier, following measles.

**d. Cases following other conditions or diseases**

*We give here the short excerpts of the cases mentioned in the literature* as perivenous encephalitis, and regarded as equivalent to typica postvaccinial encephalitis.

*Measles*

Typical microglia encephalitis is well known as post-measles complication, but explanations of other histological pictures in clinical post-measles encephalitis differ with various authors. According to many authors (Lhermitte, van Bogaert, Ferraro), other types of encephalitis or encephalopathy can occur, but B. and K. M. Walthard (1958) bring these under the same heading, either as "Toxisch-perakut verlaufenden Typus der *Masernencephalitis*" *or as* "*Spät*fälle". Jacob (1936) also groups together the cases with different pathology As will be shown later, we think that a sharp distinction should be made here

Measles is often complicated by haemorrhagic pneumonia or *bronchopneumonia and this may* be expressed also in the reaction of the central nervous system. more lymphocytic infiltration and sometimes haemorrhages in the foci.

*German measles, rubella*

*The number of cases with autopsy report is* very small; we will give a short report on the cases *that have been laid down in* the literature

as perivenous encephalitis by their author, or in discussions on this subject.

*Case of Tinel and Bénard*, 1923. Man, 21 years. Died 6 days after eruption of exanthema. Spinal cord examined, revealed rather typical microglia myelitis.

*Case of Briggs*, 1935 Boy, aged 10 years. Two days after exanthema cerebral symptoms set in, with convulsions and death within 24 hours Perivascular lymphocytes and leucocytes, other foci haemorrhagic. No microglial reaction The boy suffered of haemorrhagic pneumonia. The case is evidently not one of microglia encephalitis, but a toxi-infectious process.

*Case of Wigand*, 1941. Boy, aged 10. Had status thymico-lymphaticus and suffered from otitis Three days after eruption of exanthema nervous symptoms developed, then convulsions and death Brain swollen; vascular cuffs with lymphocytes, some plasma cells, histiocytes and polynuclears No cells outside the Virchow-Robin space, but some oedema No demyelination Evidently this is an acute vascular syndrome but no microglia encephalitis

*Case No 117 of Moller*, 1949 Man, 20 years Four days after eruption of the rash, nervous symptoms came on; death after 3 days. Autopsy showed typical perivenous proliferation of the microglia.

*Case of Falger*, 1944 Woman, 26 years Exanthema 15 days after infection Cerebral symptoms one week later, and next day death in coma. Brain hyperaemic, perivascular cuffs with lymphocytes and glia, mostly in white matter Some vessel wall changes Description is insufficient for exact evaluation but might have been microglia encephalitis.

*Varicella*

Of six cases which have come to autopsy we can give the following details

*Van Bogaert* (1930) Girl, aged 12 Had angina, a week later varicella eruption After one day cerebral symptoms, and death 18 days after the eruption The foci are not typical of microglia encephalitis but, as van Bogaert remarks, resemble those of acute multiple sclerosis.

*Zimmermann and H. Yannet* (1931). Child, 13 months old. Fever three days after the outbreak of the rash; next day a convulsion and death. Brain some oedema. Microscopically, marked ganglion cell degeneration; petechial haemorrhages. In white matter foci around veins, with fatty granule cells and demyelination. No microglial proliferation. Evidently an acute vascular encephalopathy.

*Dagnélie and Dubois* (1932). Girl, 8 months. On 15th day after eruption cerebral symptoms started. Coma and death after 24 hours. Brain hyperaemic. Perivascular demyelination with sharp borders; some fatty granule cells; no other cellular infiltration.

These 3 cases do not belong to the group of microglia encephalitis; two showed the typical toxi-infectious reaction of young children, and van Bogaert's case belongs to a very different group The following case, which we know only from references, seems to be positive.

*Roeder-Kutsch* (1944, description by Walthard, 1958). Boy, aged 7. Started with cerebral symptoms 10 days after the eruption and died 8 days later. The description and the figures have the typical features of microglia encephalitis.

*Swan* (1946) Boy 6½ years, had varicella and angina, and started 8 days after the onset with nervous symptoms, spasm, sopor, convulsions, with remissions and exacerbations. Died of bronchopneumonia 4 weeks after eruption of the exanthema. Clinical diagnosis was tetanoid chorea, as post-varicellar encephalitis. Pathological examination showed symmetrical softening in the neostriatum and more diffuse vascular and perivascular lesions, with softening and some demyelination Ganglion cells disappeared All forms of glia cells increased. Evidently we have a vascular affection, not the result of microglia encephalitis

*Appelbaum et al.* (1953) briefly mention one case, without giving details, showing perivascular oedema and lymphocytes.

*Smallpox*

Cerebro-spinal symptoms following smallpox are not frequent but, when they do occur, the disease is often serious

*Spiller, case 2*, 1903, 1929. Developed symptoms of myelitis and died about 5 weeks after smallpox eruption. Lesions mainly in grey matter, resembling poliomyelitis, but in 1929 compared with perivenous encephalitis. Description, however, not typical. Patient had septic condition. The case cannot be considered one of microglia encephalitis

*McIntosh and Scarff* (1930). Child, 2 years old, showed perivascular demyelination, with cells in the space of Virchow-Robin but no microglial reaction.

*Troup and Hurst* (1930). Man, 63 years, had alastrim, duration 37 days; total transverse myelitis, decubitus, cystitis, lung complication. Total malacia of lumbosacral cord, in higher centres gradually less severe lesions. Around the latter often typical microglial foci, with demyelination, generally with lymphocyte cuffs The entire brain showed vessels surrounded by lymphocytes, but microglial foci were very rare, only in the higher centres.

*Marsden and Hurst, case 1*, 1932 Alastrim epidemic 10 years old, death 14 days after the illness started Description typical of microglia encephalitis but severe degeneration of motor horn cells in lumbar cord

*Case 6* Girl, aged 7, died 9 days after onset of the illness. Typical lesions in the brain, spinal cord less markedly affected Rather thick lymphocyte cuffs.

*Case 7* Boy, 13 years, died one week after exanthema eruption, after an illness of 3 days Brain showed perivascular lymphocyte cuffs around many arteries and veins, and a few foci of demyelination with microglial reaction

*Brouwer, de Jongh and Rochat* (1933) See also Chapter 4, c Man, 27 years Revaccinated during incubation of smallpox Had mild exanthema but continued his work, until acute transverse myelitis set in 5 days later Death 2 months after onset Main lesions in spinal cord, very few in oblongata, pons, basal ganglia, none in the hemispheres Demyelination is often perivascular, with lymphocytes and syncytial microglial increase, and many fibrillar astrocytes Some fatty granule cells The case can be considered one of microglia encephalitis, in which partial healing of many foci took place, whereas in others complications arose due to a septic condition

*Influenza, angina, common cold*

*Greenfield, case 1*, 1930. Man, 37 years old, suffered from bronchopneumonia which improved in 18 days. After some exercise he developed the first symptoms of transverse myelitis the same evening; he died 6 days later (with bronchopneumonia). Autopsy revealed typical microglial foci in the cord and brain.

*Case 2.* This case showed no microglial foci, only lymphocytic infiltration. The distribution in the cord was rather typical, but foci were absent in the brain and brain stem. As the cerebral illness lasted 40 days, it is possible that microglial foci had already healed, while the lymphocyte reaction remained much longer. A definite evaluation, therefore, is impossible.

*Demme, case 1*, 1930. Man, aged 21, suffered from recurrent angina. Day after bathing in very cold water, acute onset of headache and meningeal symptoms with cranial nerve involvement. Gradually spreading of paralyses and death from bulbar symptoms on 10th day of illness. A rather large focus was found in the oblongata, with central necrosis, probably not the result of many coalescent foci. Some vessels in the vicinity showed lymphocyte cuffs and microglial infiltration with demyelination, mostly around very small veins or capillaries. The distribution is mainly in the oblongata; less in the pons and still less in the mesencephalon. The description and the figures suggest disseminated encephalomyelitis, or even poliomyelitis, rather than microglia encephalitis.

*Davidson and Brock, case 1, 1937.* Man, 37 years, died from decubitus and septic condition 41 days after a common cold, followed by cerebral involvement lasting 3 weeks. Clinically some improvement of the neurological symptoms was noted before death. Many foci of demyelination without cellular infiltration were found, often with fatty granule cells and astrocytes. It is doubtful whether this case has been a partially healed microglia encephalitis or, more probably, a toxi-infectious vascular condition.

*Davidson and Brock, case 2.* In this case the illness lasted 6 days, starting with general symptoms for 3 days. The patient had an

abscess in the prostate and inflammation of the testicles. The brain was large, 1565 g, and showed many small round areas of demyelination, with lymphocytes, but without typical microglial proliferation. This was probably a case of toxi-infectious vascular disease.

*Moller, case 2*, 1949. Man, 26 years old. Two weeks after a catarrhal infection acute nervous symptoms set in, with death following 2 days later. Many foci were found in the C N S, mostly around paracapillary vessels. No further description is given, but the case may be interpreted as microglia encephalitis.

*Crome* (1954) describes two cases of influenza with haemorrhagic encephalitis. Around some foci microglia can be seen. All types of lesions are considered by the author to belong to one group.

*Rabies*

The pathology of rabies encephalitis is quite different from that of microglia encephalitis (Schukri and Spatz and others), but two cases are on record in which rabies developed in the course of antirabies treatment and in which some microglial foci were found at autopsy.

*Higier* (1912). A girl, 12 years old, started antirabies treatment the day following a bite by a probably rabid dog. Received 5 daily injections, then desisted because of fever. Twenty days after the trauma, the first symptoms of rabies were noted; death within 3 days. Animals injected with brain material died of rabies. Pathology of rabies was found in the cord: lymphocytic infiltration, Babes' glial nodules, but Negri bodies were absent. In addition foci were found of, and photographs showed microglial proliferation in the parenchyma around vessels, with lymphocyte cuffs in the Virchow-Robin space. The description is suggestive, but not quite typical, of some perivenous microglial foci, nothing is noted about demyelination.

*Rojas* (1932). A man was bitten by a rabid dog and received antirabies injections from the 23rd to the 38th day. On the 37th day, the first changes of rabies were noted, he died on the 42nd day. The clinical course had been typical, inoculations in animals were positive and Negri bodies were found in the brain. The inflammatory changes

occurred in the grey matter; the cerebral white matter was free; Babes' nodules were present. Then other foci of perivenous microglial proliferation were found, without lymphocytes.

*Antirabies treatment*

Transverse myelitis, occurring during antirabies treatment, or starting shortly after it, has been known for a very long time. In 1912, however, Pette distinguished 4 clinical types of nervous disorder, *viz.*: the myelitic type; the encephalitic type; the optic and the neuritic type. The main localization was in the grey matter; some foci showed the typical perivenous microglial type.

*Bassoe and Grinker, case 1*, 1930. Woman, 48 years, was not bitten by a dog. She had received 14 daily injections of antirabies vaccine when symptoms of a Landry paralysis started. She showed no cerebral symptoms. Death came on the 42nd day after the first injection, from decubitus ulcers and bronchopneumonia. Autopsy showed absence of foci in the brain, but extensive destruction of the spinal cord, with lymphocyte cuffs, microglial proliferation, fatty granule cells and some demyelination The case differs from pure microglia encephalitis in the severe necrosis of the cord and the absence of lesions in the higher centres. Some perivascular foci, however, are typical of perivenous microglia encephalitis, and the long duration and final toxic condition could explain some of the differences. We think it is better to class the case as ±, because it shows rather important differences from our cases of postvaccinial transverse myelitis.

*Stuart and Krikorian* (1930) Man, 24 years, was bitten by a stray dog. Next day he started treatment and after the 14th injection, symptoms of Landry's paralysis set in. The disease was progressive until death on the 18th day after the trauma The spinal cord showed the typical lesions of subacute disseminated myelitis, well known as the most common complication of antirabies [illegible]

*Uchimura and Shiraki* (1957) des[illegible] of [illegible] Japan They found no microglial foci, [illegible] and demyelination and smaller foci [illegible] cells in the grey [illegible]

*Jones* (1958). Man, 58 years. Played with rabid dog. Received 14 daily injections. Two months after the first injection, acute onset with cerebral symptoms and hemiparesis. Death 16 weeks after first injection. Many foci of encephalitis were found, probably increasing in size. Jones compares his case with acute multiple sclerosis.

*Injections and vaccinations* (except smallpox and rabies vaccine)

Cerebral damage following injections or vaccinations is not very rare. Klinge (1944) reports on 45 cases in soldiers, who died as a result. Two cases were due to smallpox vaccination (with probably one case of perivenous encephalitis). The others followed antityphus, tetanus, diphtheria vaccinations, etc.

Many articles have been published on this subject and the general opinion is that perivenous encephalomyelitis does not occur in these cases.

Lhermitte, Walthard, Volland are of the opinion that typhoid-paratyphoid injections sometimes cause other types of encephalomyelitis, and this is also true for antitetanus injections (Czernely, 1950).

We found only two cases, sometimes mentioned in the literature as perivenous encephalitis.

*Giffin, Rogers, Kernohan* (1948) A woman, 21 years old, had received 3 antityphoid injections four years prior to the present illness Following a new antityphoid injection, general malaise and leftsided hemiparesis started the second day and the condition grew progressively worse. Serious cerebral involvement started one month after the injection, and was progressive until death, 4 days later Large foci of softening were found in the right hemisphere and a great many small foci in other parts of the brain These showed demyelination with central necrosis and oedema and infiltration by fatty granule cells. There was no excessive glial proliferation The nature of these foci could not be determined, but it is evident that it is no microglia encephalitis.

*Giedion* (1952) A soldier on active service received from 3 to 23 12 incl, seven injections against cholera, typhoid, paratyphoid, and was

vaccinated against smallpox on the day of the last injection. On 24.12 fever and cerebral symptoms set in, and next day he was soporous. The condition was progressive until death on 4.1. Histopathological examination showed haemorrhagic encephalitis with some lymphocytic polynuclear and glial proliferation, but no lesions of microglia encephalitis. The rôle of the smallpox vaccination is dubious and it seems unjustified to call this case haemorrhagic postvaccinial encephalitis.

**e. Subacute case**

In the literature we sometimes find the following case mentioned as a subacute case of perivenous encephalitis.

*De Massary and Albeissar* (1936) describe a patient, 41 years old, with progressive disease ending fatally in about 3 months. Clinically, mental and neurological symptoms were gradually increasing, without acute onset. No aetiological factors could be found. Autopsy showed multiple foci of demyelination in the centrum ovale, mostly around vessels, with a marked increase in astroglia and oligoglia and some increase in microglia. The diagnosis of the authors was Schilder's disease, but in the discussion Bertrand pointed out a resemblance to postvaccinial encephalitis and to senile vascular changes in the hemispheral white matter. The case can probably be grouped with disseminated encephalomyelitis of a special type, but it is certainly no microglia encephalitis.

**f. Relation of microglia encephalitis to disseminated encephalomyelitis**

The trend of this work has been to examine whether post-exanthematous perivenous encephalitis, as described by the early authors (Turnbull, Bastiaanse, Spielmeyer, Wohlwill, Spatz and others) and called by us microglia encephalitis, must be regarded as a unit with enough characteristic features to differentiate it from other cerebral reactions. A full discussion of this will be given in the next chapter.

Microglia encephalitis is one of the types of perivenous encephalitis and we think that it should not be grouped together with other types, because pathological and aetiological differences exist.

Microglia encephalitis is one of the demyelinating diseases, but here again it must be given a separate place. The cases of this group vary both in their clinical course and in aetiology and pathology.

Microglia encephalitis is a disseminated encephalomyelitis but, as pointed out, ought to have a separate place in this group.

We do not know yet which aetiological factors are important in causing the cerebral reactions of these various groups Probably some factors are the same but others are different In his excellent discussion, van Bogaert (1950) reviews a great number of borderline cases between perivenous encephalitis, disseminated encephalomyelitis and multiple sclerosis, for which a similar but not identical aetiological factor is postulated. Van Bogaert lays greater stress on the constitution and on predisposing factors than on differences in aetiology.

It will be our task in the future to determine which factors cause special types of reaction, and which influence on these reactions is played by other factors. We might then be able to divide this great group of diseases into a number of syndromes, in each of which aetiology, clinical aspects and pathology can be defined.

**g. Experimental perivenous encephalomyelitis**

The importance of multiple sclerosis, the aetiology of which has ever been a much discussed question, induced many investigators to try to solve this problem by the experimental route. Since more than a quarter of a century, many experiments have been conducted. Although the idea as a rule was to produce subacute or chronic cerebral reactions which, of course, are not apt to throw much light on our problem of acute postvaccinial damage, some experiments showed acute lesions, and it will therefore be necessary for us to establish a possible relationship with clinical postvaccinial encephalitis

Many experiments were conducted on the basis of the theory that the demyelinating diseases were due to some allergic reaction of the brain.

Another approach to our problem tried to reproduce the conditions supposed to act in postvaccinial encephalitis.

Although it has not been possible experimentally to reproduce the picture of typical microglia encephalitis, part of this picture (perivenous

microglial proliferation with demyelination) was sometimes encountered.

The focal reactions in the experiments based on the allergic theory, are generally perivascular, with localization predominantly in the white matter. Vessel-wall changes and exudation of fluid and haematogenous cells predominate; central necroses and small haemorrhages are a common feature. This, therefore, is comparable with the allergic reactions in other organs. Demyelination is often found. It is stated by all authors, that the reactions are not predictable, that the same technique can cause various types of lesions and that very little is known about the factors governing these differences. A microglial reaction is often seen, caused by degeneration of myelin, and then fatty granule cells occur in large numbers. But the diffuse perivenous microglial foci seen in postvaccinial encephalitis are rarely found. Lumsden (1949) describes these foci, running the length of some veins and without thick lymphocyte cuffs. However, he states that vessel-wall changes are nearly always present, generally with an increase in connective tissue of the adventitia.

In their summing up of recent work on experimental encephalitis, Ferraro and Roizin (1954) state that the microglial reaction is rarely seen in the subacute and chronic stages but belongs to the first stages.

The other approach, mentioned above, succeeded once in producing a perivenous microglial reaction very similar to that seen in postvaccinial cases. Verlinde (1954) started a series of experiments in which smallpox vaccination of the animal was combined with injections of various substances (guanidine, phosphatase, etc.) or inoculations of other viruses. In the case referred to, a monkey was vaccinated on the skin against smallpox and received an intramuscular injection of Columbia S.K virus, which was isolated from the stools and throat of a child diagnosed as suffering from postvaccinial encephalitis. The child was about one year old and had, 2 months prior to the vaccination, been in places where poliomyelitis and other cases of meningo-encephalitis occurred. Nine days after this procedure he had a convulsion, but recovered after treatment with ACTH and aureomycin. The diagnosis: postvaccinial encephalitis, might be correct (not microglia encephalitis

but the encephalopathic type), but another explanation is also possible, *viz.*: that the vaccination activated an encephalitis by Columbia S K. virus.

The animal developed neurological symptoms on the 7th day and died the next day. Histological examination revealed many lesions with demyelination and microglial proliferation around the veins and some lymphocytes perivascularly Some foci are quite typical, others are located in the upper layers of the cerebral cortex; some are abnormally compact Although the lesion is not a pure microglia encephalitis, the similarity of some of its foci is striking.

This lesion was not reproducible: experiments with the same ingredients, or by vaccination and using other strains of Columbia S.K. virus, failed to produce the perivenous encephalitis. In the animals that died with neurological symptoms, polioencephalomyelitis was found, as sometimes also seen following injection of Columbia virus without smallpox vaccination.

As far as a very short survey of the literature teaches us, the most frequent reaction of the brain to an experimental approach to the problem of demyelinating diseases is a vascular and circulatory change, and microglial foci without vascular reaction are rare, but they go in the same direction as following many infections diseases in man. Pure microglia encephalitis has not hitherto been experimentally reproduced.

*Chapter 6*

# DISCUSSION
# THE NOSOLOGICAL ENTITY OF MICROGLIA ENCEPHALITIS

**Introduction**

In 1950, van Bogaert wrote: "it appears as though the perivenous encephalitis found in all these diseases is a standard form of reaction in the nervous tissue". It will be the task of future research to find to *which causes and conditions the nervous tissue reacts by this standard form.*

According to the basic idea of the present study, we shall use in our discussion mostly the cases in which post-mortem examination of the nervous system has been performed. Our principal aim has been to *see whether sharp distinction should be made between the diseases* with foci consisting mainly of vascular changes, encephalopathic and haemodynamic cerebral reactions and the disease "postvaccinial encephalitis" in its more restricted sense, with foci of demyelination with microglial proliferation. Further, whether this latter disease should be separated from, or at least classed as a special type of, acute perivenous demyelinating encephalomyelitis.

Other diseases starting during the first 3 weeks after vaccination must also be considered, because some connection between their outbreak and the vaccination may exist, as found in embolic encephalitis and probably also in poliomyelitis. These conditions will not cause difficulties in our cases with autopsy, but the clinical course may very much resemble the picture of postvaccinial encephalitis.

We shall separately discuss the clinical and pathological aspects and then see whether any conclusions about the pathogenesis can be formed at this time.

**a. The clinical side**

The clinical picture of microglia encephalitis is typical. The onset is acute with general malaise and fever for one day or less, after which the cerebral symptoms become manifest. Following a severe skin reaction to the vaccination, however, fever, headache and general malaise may often exist from the 6th or 7th day on and sometimes merge into the oncoming symptoms of the cerebral complication. The exact day of onset of the encephalitis is then difficult to determine, and may be put one or two days too early. According to the main localization of the lesions, mental symptoms may prevail, or cerebral or spinal neurological irritation or pareses may dominate the picture.

The course is always acute, reaching its acme in a few days, even running a fulminant course in several cases, death following one or two days after the first symptoms were noted (see Fig. 18). In these

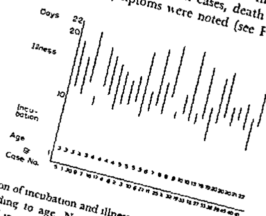



Fig. 18 Duration of incubation and illness of 28 cases of microglia encephalitis, arranged according to age. No correlation is found between age of patient and duration of incubation and duration of survival time after vaccination. Incubation varies much less than survival time.

cases, as in the others, the autopsy shows the fully developed picture of microglia encephalitis rather than the vascular, encephalopathic pictures of toxic-infectious reactions (see par. b, A 2). Table I (p. 13)

also shows that there is no correlation between the day of onset and the duration of illness, nor between these and the age of the patient.

When the disease does not run a fatal course, *some improvement* in the patient's condition can be seen, generally within a week. Some patients, surviving that long, may develop complications which increase the risk of a fatal outcome. If the patient survives, there is no *chronic stage, nor do we see sequelae or relapses. These point to* complications or to another type of encephalitis (Chapter 3, par. b, 4). Only in cases of transverse myelitis may the damage due to oedema of the cord be rather serious, and may hypertonia or pareses last for a long time.

This clinical picture can in many cases not be distinguished from other toxi-infectious brain diseases occurring after vaccination or following many other conditions. We have pointed out that much misunderstanding has arisen when too much weight was given to the clinical picture and all changes in the brain, found in these cases, were grouped together as one disease (Lhermitte, Comby and many others).

*Incubation time*

The duration of incubation is a valuable point of differentiation *between the various conditions.* The earliest investigations on post-vaccinial encephalitis have shown that the incubation lasted about 10—14 days and that exceptions were rather rare. As the following figure will show, this becomes still more convincing when we compare *the incubation in microglia encephalitis (Fig. 19)* A with B and C, giving the incubation of other cerebral complications in 0 to 1-year old children and older persons, respectively.

The number of cases in Fig 19 A is very small because only the cases with *personal microscopic examination* were used. But tables have been given by many authors, using a larger material of clinically diagnosed cases, and they show the same difference between the typical cases in persons of 2 years and older, with a rather symmetrical biphasic curve, with the maximum at *12—13 days, and those cases* with atypical course. The same holds true for the graphs pertaining to

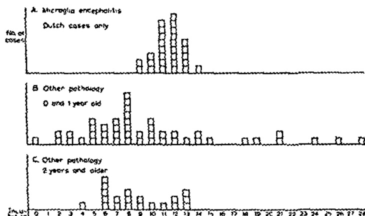



Fig 19 Incubation time of 3 groups of postvaccinial complications Autopsy cases mentioned in this treatise

very young children, which show a very irregular distribution.

Cases following measles cannot be used, as the date of infection is uncertain and as the mode of infection and the amount of virus invading the tissues may vary much more than under the nearly experimental conditions of smallpox vaccination. In cases only clinically examined, a shorter incubation time is sometimes shown, but the history then often states that convulsions developed, or that serious sequelae remained which, for us, makes it probable that not microglia encephalitis, but *e.g.* haemorrhagic encephalitis occurred.

In one case (No 9) the incubation was given as 8 days, but this boy was already under treatment for whooping cough and, in addition to the vaccination on Aug 6th, had received injections against that disease on the 9th, 11th and 13th day On that day he became ill and Aug. 14th had a mild convulsion, following which cerebral symptoms became evident The convulsion may have had a toxi-infectious origin, and the encephalitis perhaps started on the 9th or even 10th day after vaccination In other cases it may be difficult, when the history is incomplete, to evaluate whether fever and headache are the

result of the vaccination with severe skin reaction, or already the first symptoms of a cerebral complication. The graph of the incubation therefore tends to be distended to the left side, but is probably never extended further than it really is.

The difference between the first graph (A) and the second (B) is quite conclusive of the fact that microglia encephalitis is not a part of the general reactions of young children to toxi-infectious diseases but that it stands by itself. It is illogical to regard all these cases as running a fulminant course of a disease which has, in this age group, never been observed. Furthermore, the incubation period would then have to be shorter than the usual incubation for microglia encephalitis, and not distributed at random over a period of 4 weeks. In Chapter 4, b it has been remarked that the histological picture of the cases represented in Fig. 19 B is not the earliest change that could develop into perivenous microglial foci.

Comparing the graphs 19 A and C, the same holds true. If these cases were to be considered as earliest microglia encephalitis, the graph C ought to show the same variability curve as A, only shifted two or three days to the left, with the maximum at 10 days.

The typical incubation time, therefore, is a strong argument to consider microglia encephalitis a separate unit.

*Occurrence of microglia encephalitis compared with other pathological changes, and occurrence in various diseases*

From the first appearance, around 1924, of postvaccinial encephalitis and the similar complication following measles, it was apparent that exanthematous diseases play an important role. It is interesting to find out whether this also holds true for typical microglia encephalitis. It was known, of course, that other pathological changes also occurred Bastiaanse (1931) found from his clinical studies that, following 709,918 vaccinations, 138 cases of postvaccinial encephalitis occurred, and 136 cases with other cerebral affections. Too often, however, an encephalitis following vaccination was called perivenous, without realizing that it might as well be something else.

A



TABLE X

CASES OF POST INFECTIOUS NERVOUS COMPLICATIONS

Extracted from article by Moller, 1949

| *Etiology* | *Perivenous encephalitis* | *Other pathology* |
|---|---|---|
| Smallpox vaccination | 11 | 6 |
| Measles | 10 | 7 |
| Rubella | 2 | 4 |
| Varicella | 2 | 1 |
| Scarlatina | 1 | 3 |
| Parotitis | 3 | 2 |
| Whooping cough | 1 | 11 |
| Pneumonia | 1 | 7 |
| Dysentery | — | 2 |
| Tooth abscess | — | 2 |
| Otitis | 1 | 7 |
| Tonsillitis | — | 4 |
| Common cold | 1 | 1 |

We will first discuss the interesting reports of Moller, on post-infectious nervous complications in Sweden, and then investigate our own material in this respect

From the literature and from personal examination Moller (194 listed a large number of cases, of which our Table X was mad Differentiation between microglia encephalitis and other forms c perivenous encephalitis was not possible, but the table very clearl indicates in which diseases we may expect the microglial reaction tc occur with more or less frequency In the column of perivenous encephalitis, the following cases are listed by Moller common cold, Moller 1949, otitis, Brissaud and Brécy, pneumonia, Adler, 1940, whooping cough, Moller, parotitis, Scheinker, Wegelin, Donohue, scarlatina, Ferraro, 1944 Of these, we accept only 2 cases as microglia encephalitis (Moller, common cold and Donohue, parotitis) Several of her other cases do not even show perivenous microglial cuffs, according to her description The table clearly shows that a

*common toxi-infectious reaction of the brain* is a more frequent reaction following most diseases, but is also very common after the four exanthematous diseases.

From our study of the literature we made Tables XI and XII. These show various interesting details (the distinction between microglia encephalitis and perivenous microglial foci will be discussed in the next paragraph).

Only following smallpox vaccination in persons of 2 years or older does the microglia reaction occur more frequently than the toxi-infectious reaction types. In all other conditions we find more cases of the other reactions than of microglia encephalitis. *Here the occurrence of microglia encephalitis is only sporadic:* parotitis; influenza; anti-rabies treatment; cases without clear aetiology, or very late after vaccination. *We believe that these sporadic cases also occurred before the massive* outbreak after 1923. Perhaps even the relative frequency of occurrence of microglia encephalitis and other pathological changes has, for the above enumerated diseases, not changed significantly since that year, which would mean that the frequent occurrence following exanthematous diseases really was new, which was the general impression of most clinicians and also stated by various authors for the pathological anatomy (Bastiaanse, Lucksch, Spielmeyer).

Looking at one special aetiological feature, we can make the following lists (Table XIII).

*It is at once evident that the occurrence of microglia encephalitis does* not follow a random distribution but that some relation between its frequency and the special type of infection exists. Especially the fact that it develops after pox virus infections inversely proportional to the seriousness of the disease, must be stressed. We could think of the influence of stress on the pathogenesis of these conditions. A possible explanation could be that, in the more serious disease (small pox, as opposed to alastrim or vaccinia), the *adaptation reaction* would be stronger and therefore give an increased production of ACTH or cortisone, which would suppress eruption of an encephalitis. Clinical *data about the therapeutic influence of cortisone injections in the* earliest stages of postvaccinial encephalitis, support this theory.

## TABLE XI

AUTOPSY CASES DESCRIBED IN THE LITERATURE AS PERIVENOUS ENCEPHALITIS

Revaccination includes own cases. — No case known + more than a few cases

| | | *Microglia encephalitis* | *Perivenous microglia foci* | *Toxi-infectious reaction* | *Encephalomyelitis dissem. acuta* |
|---|---|---|---|---|---|
| | following vaccination | — | 1 | + | |
| Before 1923 | following rubella | 1 | — | | |
| | without clear etiology | 1 | 1 | 1 | |
| Primary vaccination, 2 y and older | | +++ | — | + | |
| Revaccination with good pustules | | 8 | 3 | 8 | |
| Primary vaccination, 0 and 1 y old | | — | — | +++ | |
| Revaccination with immune skin reaction | | — | 1 | 4 | |
| Mild smallpox, alastrim, cowpox | | 4 | 2 | | |
| Heavy smallpox | | — | — | + | |
| Measles | | ++ | | ++ | |
| Rubella | | 2 | — | 2 | |
| Varicella | | 1 | — | 4 | |
| Parotitis | | 1 | | | |
| Rabies | | — | — | + | |
| Rabies outbreak during antirabies treatm. | | — | 2 | | |
| antirabies treatment only | | 1? | — | | +++ |
| Vaccination + typhus inj 1 month before onset | | 1 | | | |
| Influenza, angina | | 1 1? | | ++ | |
| Poliomyelitis | | — | 2 | | |
| Pertussis, scarlet fever | | — | — | +++ | |
| Other vaccinations and injections | | — | — | +++ | |
| Etiology unknown | | 2 | 4 | +++ | |
| Experimental | | — | ++ | +++ | +++ |

## TABLE XII

PERIVENOUS ENCEPHALITIS CASES FROM THE LITERATURE GROUPED ACCORDING TO PATHOLOGY

Condensed from preceding table. Only about 50% of the cases described in the literature as perivenous encephalitis are probably microglia encephalitis

| | *Microglia encephalitis* | *Perivenous microglia cuffs* | *Other pathology* |
|---|---|---|---|
| All cases except vaccination, measles, rubella, poliomyelitis, but including smallpox | 13 | 7 | 20 |
| Same, but excluding also smallpox, varicella | 8 | 5 | 12 |

## TABLE XIII

COMPARISON OF THE FREQUENCY OF MICROGLIA ENCEPHALITIS AND OTHER PATHOLOGICAL CHANGES IN TWO GROUPS OF NEARLY RELATED DISEASES

| *Exanthematous diseases* | *Microglia encephalitis* | *Perivenous microglia cuffs* | *Other pathology* |
|---|---|---|---|
| Vaccinia, over 2 years old | +++ | | + |
| Measles | ++ | | ++ |
| Rubella | 2 | | 2 |
| Varicella | 1 | | 4 |
| *Pox virus infections* | | | |
| Primary vaccination | +++ | — | + |
| Revaccination, good pustules | 8 | 3 | 8 |
| Mild smallpox, cowpox, alastrim | 4 | 2 | |
| Heavy smallpox | — | — | — |
| Revaccination immune reaction | — | 1 | 4 |

It is stated by some authors that postvaccinial encephalitis occurs more often in those countries in which anti-smallpox vaccination is regularly performed, and that in countries in which smallpox is endemic, the encephalitis is absent or very rare. We have no data pertinent to this question.

A short discussion of cases following *revaccination* may follow here, but this has been more fully treated in Chapter 4, c. When revaccination is followed by a normal skin eruption, microglia encephalitis occurs less frequently than after primary vaccination, and other forms of encephalitis are relatively more frequent.

When the skin still shows some immunity to the vaccinia virus, a typical microglia encephalitis has never been observed but very irregular histopathological pictures may be seen, in which demyelination and microglial proliferation around vessels are sometimes present. We have at present no explanation for this phenomenon, but it is evident that the condition of partial immunity must have caused a severe change in the constitution of the body fluids or cells, by which the demyelinating factor cannot develop or act as after primary vaccination.

Another important point in the variations in occurrence of microglia encephalitis is the *absence in children of 0 and 1 year of age.* This has been fully discussed in Chapter 4 b, to which the reader may be referred. We pointed out, that the majority of the infectious diseases can attack children under 2 years of age as well as older persons, but that the two groups differ in sensitization and allergic reactions. The reactions seen following vaccination in these young children are of the common toxi-infectious type, occurring in all age groups and after a great many toxic and infectious conditions, probably in the young children not more frequently after vaccination than after common cold, angina, fever and the like.

Our material is not large enough to calculate the importance of age as a factor in the eruption of microglia encephalitis (except for the first 2 years of life) It is often stated in the literature that children from 3 to 12 years should be more vulnerable to this disease, but the number of vaccinations in the different age groups varies in many countries, which makes comparison rather difficult

The same can be said about the geographic distribution. It is well known, that postvaccinial encephalitis is more common in western Europe than elsewhere, and that it is very rare in tropical countries. Uiberall (1950) found in Chile, among one million vaccinations, only 15 cases of cerebrospinal complications. In New York, Greenberg and Appelbaum (1948) found, after 5 million vaccinations, 49 cases of encephalitis which were certainly not all of the perivenous type.

There is also a wide variation in the frequency of perivenous encephalitis in different years (Goeters and Stechern, 1938; Falk, 1950, and others), which is also known for other diseases (Greenfield, 1929, for measles); its bearing on our subject will be very difficult to understand.

Brief mention should also be made of *subclinical cases*, because sometimes the literature contains reports with the tendency to regard very mild cases of encephalopathy as subclinical perivenous encephalitis. As far as our discussion is concerned, this pertains mainly to the cases in which death came on without a clinical period of disease. An investigation of E.E.G. changes in persons without any clinical symptoms of a cerebral nature was done by van Wulfften Palthe and Puister (1956). They found that, of 40 healthy military men, 14 showed a change in the E.E.G., taken in these subjects before vaccination and one half year later. None of them showed clinical changes, or developed subsequent postvaccinial symptoms. The authors come to the conclusion that the general vegetative condition in these persons undergoes a temporary *and reversible change in the sense of* increased lability.

In measles, Hode and Livingstone (cited by Radermecker, 1956) found an abnormal E.E.G in 43 of 114 cases without cerebral complications (none of these under one year old), suggesting what they call subclinical encephalitis

Brown, Kirkland and Hein (1948) reported on the spinal fluid examination in 70 cases of parotitis: in 26 cases they found more than 10 cells, only 9 patients had mild cerebral symptoms (one case of *meningo-encephalitis also had orchitis*). They then examined the spinal fluid in 5 cases of measles in adults, and found 26, 14, 11, 2 and

o cells, respectively. Only the patient with 26 cells had slight cerebral symptoms. Cronemeyer (1957) found pleocytosis of the C.S.F. in 25% of measles patients and in 32% of varicella cases without any clinical symptoms of nervous system affection.

It is well known that infectious diseases attack the entire organism and not exclusively one or two organs, and it is very difficult to state when a change in the spinal fluid is sufficiently marked to speak of a meningeal or cerebral complication. That this may be present without clinical symptoms may explain those cases, in which a rapidly developing cerebral oedema (in young children perhaps accelerated by status thymico-lymphaticus) may cause sudden death. *But nothing points, as far as our study has revealed, to a perivenous encephalitis being at the origin of it.*

**b. The pathological side**

In our discussion of this aspect or our problem we shall use the following scheme as a working hypothesis:

*Vaccination* against smallpox is followed by *vaccinia*, which is a general disease of the entire organism. This means that we can expect the reactions often encountered in toxi-infectious conditions

A. (1) always more or less serious irritation of the reticulo-endothelial system, which in the C.N.S. can be seen as a very slight cellular increase in the spinal fluid, some degree of lymphocyte infiltration of the meninges, probably some hyperaemia and perhaps some oedema. This may start at an early date

(2) In few cases an exaggeration of this can occur, which can be clinically diagnosed as encephalopathy or encephalitis, and pathologically as toxi-infectious changes of the vascular-mesodermal tissues, sometimes with ganglion cell degeneration. This probably also starts before the skin reaction is at its maximum

Then we sometimes find another type of pathological reaction, which we should sharply separate from the first

B. In some aetiologically probably very specialized instances (of as yet unknown origin),

(1) perivenous production of a myelolytic substance, which secondarily gives rise to microglial proliferation and some oedema. Probably the microglial proliferation is partly also a reaction to the noxious substance which causes the demyelination. Clinically, this produces the picture of encephalitis.

(2) This inflammatory process causes fever and general symptoms and can also cause irritation of the reticulo-endothelial system of the brain, increasing the existing changes as noted under A.

C. Finally we sometimes meet abnormal pathological reactions, which occur in rare instances and have not yet been classified. Others *show a pathology belonging to other diseases (activation; purulent* complications, etc.). These have been discussed in Chapters 4 and 5.

*Ad. A. 1.* It would at first sight seem impossible to get autopsy material from this group because when the child (or adult) dies of this disease, it is already a cerebral complication and is placed by us in group A. 2. But a number of young children and even adults sometimes died during, or shortly after, a convulsion, or were found dead in their beds without having shown cerebral symptoms before. We discussed this group in Chapter 4, e (see Table VIII) and concluded that the very slight meningeal and vascular changes were an encephalopathic reaction to the vaccinia in individuals predisposed to this kind of reaction. Radermecker (1958) sums up a number of factors predisposing to convulsions. former brain lesions; infections, anoxia; constitutional vasomotor lability; disturbance of the haemato-*encephalic barrier, etc., to which we would add spasmophilia* In many cases, therefore, convulsions are a symptom not of cerebral disease but of a general disease.

The point can be illustrated by the following case.

*Case No 48* This girl was born 16. 10 50 and was healthy before vaccination on 24 1 52 Pustules developed slowly, but were quite distinct on the 9th day without however, redness of the surrounding skin On 3. 2 she developed some fever, vomited at night, then became soporous and died on the 11th day after vaccination, with a temperature of 42°, early in the morning of 4 2 The general autopsy showed a few infiltrating cells around a coronary artery; the

spleen was normal, whereas liver and kidneys showed a distinct reticular reaction with small-cell infiltration in the periportal spaces. The meninges were [illegible] and contained a diffuse increase of small lymphocytes with a few

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apparent, the pathology showed more distinct changes of the same character as in the former groups. Still more conspicuous changes are seldom seen after uncomplicated primary smallpox vaccination, but are frequent after other vaccinations or infectious diseases (measles, scarlet fever, whooping cough, etc.). These changes, *viz.*: marked oedema of the brain with serous or cellular perivascular infiltration, with haemorrhages and distinct vessel wall changes, *sometimes with* thrombosis of vessels, are the pathological expression of what is called the "haemo-dynamic reaction" by van Bogaert; the "syndrome malin" by Alajouanine; the "orage vasculaire" by Cathalea. Pagès (1952), de*scribing toxicoses of babies, especially following enteric disturbances*, distinguishes several degrees of seriousness and says that in the most marked cases some glial increase (as also noted in our Table VIII) can be found.

In a recent article Verhaart (1958) describes the histopathology of encephalopathy, in cases of severe cerebral symptoms, accompanying general diseases in infants and children. He stresses the fact that the pathological changes are the same, independent of the aetiology of the general disease.

A differentiation of these histopathological changes into various types is not pursued in this study. However, we feel that in the future this will be necessary for a full understanding of the reaction types of the nervous system. As mentioned Jacob (1955) isolated the group of *acute diffuse lymphocytic encephalitis* as one reaction type, of which he gives several examples.

We wish to summarize here some conclusions of the important experimental work done by Lumsden (1949). Lumsden divided the pathological changes occurring in guinea-pigs after injections of brain emulsions and adjuvants, into four groups: (a) toxic reactions; (b) sensitization; (c) an immunity reaction and (d) the encephalitogenic effect He then finds that these 4 reaction types are not obviously associated, in fact, appear to be dissociated and need not even occur in the same animals

*But in none of our cases, or in any description of cases in the literature, do we find an indication that changes suggesting an early stage of perivenous microglia encephalitis were also present in the other reaction types.*

Even such authors as interpret their encephalopathic findings as first stages of perivenous encephalitis (de Lange, Lhermitte, Doring, a. o.) expressly state that the actually present changes were of another nature. And we can add to this that they also showed another distribution in the C.N.S., *viz.*, involvement of the cerebral cortex as part of the picture.

Some cases of more serious vascular reactions (haemorrhagic or embolic foci) may show pictures of perivascular demyelination and glial reaction which, at first sight, resemble microglia encephalitis. Fig. 16 shows a focus due to fat embolism (a), as compared with a microglial focus (b). In (a) the focus is round, not elongated along the vessel; it has a necrotic centre and very little glial reaction, while fatty granule cells and myelin débris are still lying around (not clearly seen in the Nissl stain). The microglial focus (b), however, is oval with much wider distribution of glia cells and without the vessel-wall reaction or necrosis. In describing case 53 (Chapter 3, b) another example of the difference of the vascular foci was given.

*But even elongated microglial foci can have another pathogenesis*, which is illustrated in Figs 20—23, of a man, 42 years of age (No 5373), who had suffered a cerebral contusion 3½ months before death. He was unconscious for about one hour after the accident and improved in the first week Then coma once more set in, due to a subdural haemorrhage, the remnants of which were found at autopsy. The condition was complicated by a fracture of the femur and developing decubitus He died of the septic condition, but had shown some dementia and irrational behaviour Autopsy showed a thin covering of the inner surface of the dura with phagocytes, containing large amounts of blood pigment Some atrophy of the brain was found Subcortically at several places, demyelinating lesions, arranged around bloodvessels, with marked glia proliferation (see Fig 20—23) existed However, the myelin stain showed also one larger degeneration, in which much iron pigment could still be observed The smaller lesions did not show a positive iron reaction, but a small haemorrhage could easily be absorbed without pigment deposit Nearly all the axis cylinders have also disappeared in these lesions, which is uncommon in microglia encephalitis

The vessels showed more changes and serous oedema was present in the smaller and larger foci and the infiltrating cells were partly large astrocytes, partly rod cells and small round glial nuclei There were no small lymphocytes, no polynuclears and very few granule cells, but some sudanophile granules were still present



Fig 20. Traumatic destruction of nerve fibres; several perivascular foci and one large long lesion. Case 5373. Weil stain.



Fig. 21. Same case as fig 20, subcortical white matter; only smaller lesions. Weil stain.

The resemblance of these foci, due to contusion of the brain, to the true perivenous microglial foci is evident, but they differ enough to put them in a separate class This again stresses the necessity of sharply distinguishing between microglia encephalitis and microglial foci of different origin.

*Diffuse ganglion cell degeneration*, often most marked in the cerebral cortex but also present in lower nuclei (subst. nigra; inferior olives) is also a common abnormality in toxic encephalopathic brain diseases but, as this may be caused by a complicating bronchopneumonia and is often rather difficult to evaluate in human material, it does not generally add a valuable argument to differential diagnosis.

*Ad B. Which is the nosological place to be given microglia encephalitis?* In the course of our investigations, it became apparent that a division of microglial proliferation into 2 types would be advantageous to our understanding, namely: the complete picture of microglia encephalitis, and the perivenous microglial foci without the other typical symptoms or changes, but often combined with vasculo-mesodermal changes in another localization.

In the first publications on this disease by Turnbull and Bastiaanse, both in 1924, the idea prevailed that a disease entity existed, which should be separated from other conditions but clinically showing some



FIG 22 Same case as fig 20, very little cellular reaction Nissl stain



FIG 23 Same case as fig 20, Iron pigment (black dots) around a large vessel near the malacic foci Gomori stain

similarity to it. Later work showed that one histological change, *viz.* perivenous microglial proliferation, also occurred in a number of other diseases and could be reproduced by experiment (Lumsden's fourth group). But these never formed a unit and therefore it is still necessary to differentiate these conditions.

The entity first described by Turnbull and by Bastiaanse, and described by Lucksch in his first publication (1924) as a change in the pathology of epidemic encephalitis due to the presence of vaccinia virus, was called *perivenous encephalitis* by Spatz. We used the name microglia encephalitis for the cases verified by autopsy. Both names, however, do not express exactly what is meant by them, because around embolic and haemorrhagic foci the microglia is also often increased and demyelination is present, and because differentiation from disseminated encephalomyelitis may be rather difficult. *It might therefore be advantageous to introduce the name disease of Turnbull, Lucksch, Bastiaanse to the clinico-pathological disease entity sometimes following smallpox vaccination and meales, and seldom occurring spontaneously or after other infections.*

The main idea underlying the necessity to make this distinction is based on the principle that we should try to determine the cause for evident differences of the reaction of the nervous system in various conditions, and not be content to speak of intermediate types or transitions without trying to explain their pathogenesis. The perivenous microglial foci are a typical reaction of the nervous tissues to some noxious condition as yet unknown. This reaction occurs in a number of diseases, the principal instances of which we reviewed in Chapter 5. The clinical side of this problem has been discussed in this chapter in par. a.

As typical histopathology in microglia encephalitis, we mentioned (Chapter 5, p 114) the perivenous microglial foci with marked demyelination and less destruction of the axis cylinders; the marginal gliosis by microglia cells and sometimes more diffuse glial increase in white and grey matter. Distribution of the lesions in the hemispheral white matter and in the white and grey matter of the deeper structures Then, sparing of the ganglion cells and small or no lymphocyte cuffs. As negative signs we noted: no necrotic centre and no thrombosis of

vessels; rare polynuclears and no coalescence to foci in which the original perivascular distribution is no more recognizable

This picture can be influenced by preceding brain diseases, an example of which may be mentioned here (case 38), in which an old lesion around the occipital horn of one lateral ventricle existed, with a dense conglomerate of ependymal cells and a broad zone of sclerotic tissue around it. This again was surrounded by a great number of perivenous foci, widely coalescent, but of the typical constitution and marked lymphocyte cuffs in the vessel sheaths. Some haemorrhage had also occurred in this region. The impression was gained that the older lesion had left the tissues more vulnerable to the encephalitic process Van Bogaert gave an example of this kind of strong reaction in the spinal segment of a patient, who previously sustained a trauma of this part of the cord. Van Bogaert calls this a *neuro-allergic reaction* due to a kind of "memory" of the involved parts.

The perivenous microglial foci, however, are known to occur in several diseases, often as a rare and minor detail (*e.g.* in poliomyelitis), or as an important part of the histological picture (disseminated encephalomyelitis). They are conform group d. of Lumsden (see above).

In Chapter 3, f, we noted cases in which noxious factors might possibly have had some influence on the histological picture of post-vaccinial encephalitis. Our material here is rather scanty and does not seem to allow of well-founded conclusions.

We now have to *consider microglia encephalitis in its relation to other encephalitides.* Only the acute forms have to be discussed, either the acute diseases or the acute phases of more prolonged diseases (multiple sclerosis and others)

*From the histological angle*, the lymphocytic encephalitides (as poliomyelitis), greatly differ from our disease. The inflammation attacks the grey substances more than the white matter, and ganglion cell destruction is the rule, myelin destruction exceptional. Then, infiltration around vessels is mainly by thick cuffs of lymphocytes and other mononuclear cells, mostly without a marked glial reaction in the

*surrounding tissue.* Around the focal lesions in the grey matter, microglia cells often proliferate, together with astrocytes. However, they are not grouped around venules or veins. Even the first authors writing on postvaccinial encephalitis stressed the differences from epidemic encephalitis, at that period the best known type of non-purulent inflammatory reaction of the C.N.S. Only few authors (Gins, 1931, 1934) tried to explain postvaccinial encephalitis as an epidemic *encephalitis with a reaction of the nervous tissue, changed by the* presence of another virus.

The group of so-called *nodular encephalitides* (*viz.* typhus encephalitis, St. Louis encephalitis) differs from the post-exanthematous group in the size and distribution of the foci. There we find nodules of glia cells, mainly microglia, of round shape, not connected with vessels and localized both in the grey matter (cortex and deeper structures) and in the white substance, or even predominantly in the grey matter. Marginal gliosis is unimportant and demyelination is not part of the picture, but vessel-wall changes and infiltration of the meninges with cellular cuffs and more diffuse infiltration can be very marked.

The *embolic encephalitides* (*e.g.* those due to haemolytic streptococci, listeria, also to fat droplets, etc.) also give another picture. Here, the capillaries are often infected and ball-shaped masses of polynuclears, often mixed with other phagocytes, are lying in the various tissues There may be necrosis of nervous tissue, with necrosis of the nerve fibres (myelin and axis cylinders) and a glial reaction to this, consisting partly of microglia and partly of the other types of glia cells. Sometimes we find a very small central focus with larger microglial proliferation, as demonstrated in Fig. 16 of fat embolism, or often seen in haemorrhagic encephalopathy (Fig. 13). But the difference from typical microglial perivenous foci is generally easily demonstrated and the other findings of microglia encephalitis are always absent in these cases.

More important, however, is a discussion of the *disseminated encephalomyelitis group* We can best understand these by considering microglia encephalitis to be one extreme of a larger group of pathological

B

changes, probably the result of various combinations of a number of pathogenetic factors similar, but not the same for the various clinical types or diseases Multiple sclerosis and the large single foci of Schilder-Foix's encephalitis periaxialis, are examples of other extremes. But this does not mean that each type loses its individuality and could not be considered a disease entity. On the contrary, when enough arguments can be brought forward to separate microglia encephalitis from the other forms, our conception of the pathogenesis and aetiology can be more firmly established and clarified Probably the number of pathogenetic factors acting together in microglia encephalitis is smaller than in other forms of encephalitis and we therefore called it (1955) the most monomorphous type of encephalitis that occurs.

The large number of foci and their obligatory distribution around veins of medium and large size at once distinguishes this type from the acute changes in multiple sclerosis and disseminated encephalomyelitis, in which a focus may start around a small vessel but then increases without following the vascular territories Also the histopathology is different, because microglia encephalitis shows only a slight reaction of the other tissues (mesodermal and other glia cells), whereas these are generally quite evident in the aforementioned diseases But in these cases typical microglial foci may sometimes be found (see Fig 158 of Pette, 1942, in a case of acute multiple sclerosis), pointing to a similarity in the pathogenesis of these foci in both diseases. Then the other histopathological changes (*e g* the marginal gliosis) are not a part of disseminated encephalomyelitis. The very acute course, the high percentage of fatal cases and the recovery of the others, without scar formation, are outstanding characteristics for the entity called microglia encephalitis.

Very few cases occur with multiple foci of perivenous demyelination, in which the myelin stain shows great resemblance to the postvaccinial encephalitis But a more chronic course and marked mesodermal cell increase point to another nosological place However, we mentioned in Chapter 5 (Table XI) some cases, which we classed with microglia encephalitis with an aetiology differing from the usual one At the present time they cannot be classed definitely and these exceptions

will not detain us from placing microglia encephalitis as an entity in the nosological system.

When we tackle the problem of the relation of microglia encephalitis to other encephalitides from an *aetiological angle*, we can at once say that the pathology differs from the diseases caused by a known virus. In the first group (Heine-Medin; lethargic encephalitis; rabies; herpes encephalitis; zoster) the difference is quite evident, as it is in the group of spring-summer encephalitides (Japan B; Australia; St. Louis, etc.). Finally the encephalitis in other virus diseases (Armstrong choreo-meningitis; encephalomyocarditis; encephalo-dermatomyositis; rare cases of encephalitis due to Coxsackie virus) differs widely from our picture. No known virus causes changes in the brain, comparable to microglia encephalitis.

The encephalitides caused by other living agents do not cause any difficulty in differentiation from microglia encephalitis, because the acute inflammatory changes generally consist of very marked infiltration by polymorphonuclears and lymphocytes of various kinds, localized in the Virchow-Robin spaces or in nervous parenchyma, when this is markedly degenerated or even necrotic.

We have reached the conclusion that microglia encephalitis is not directly caused by a living agent, but that another mechanism must play some rôle in the production of the histopathological changes.

On this point, we agree with the majority of the authors and naturally our thoughts are going in the direction of *an allergic pathogenesis* but, before discussing this, we wish to see on which pathological details a discussion can be, or must be, based.

**c. The pathogenic side. Some further considerations**

In our discussion we have opposed the vascular processes mainly occurring in the walls of and around capillaries and small vessels, to the perivenous processes occurring partly in the Virchow-Robin spaces and mainly in the parenchyma around these. The first reaction is typical of the toxic processes caused by heavy metals, organic substances and bacterial toxins and of the usual experimental procedures to produce allergic encephalitis.

c

The second, the perivenous type, follows exanthematous diseases and those experimental procedures which have either used white matter of the brain as antigen or in which vaccinia virus was introduced into the animal.

This poses the question: What is the *rôle of the veins* in this process? Is it the special type of vessel, or the space around it that is of importance?

The similarity of the subpial gliosis with the picture of the perivenous foci strongly suggests the same function, which in the former system must mean either absorption from the C S.F or excretion into it, or building up a shield against noxious substances This would bring us to the assumption that the perivenous localization of the foci points to a greater importance of the contact with the perivascular fluid than with the vessel itself This theory is supported by the fact that foci are never localized around capillaries, which do not have a perivascular space, and seldom around arteries in which this space is smaller (as seen in perivascular oedema!). The preference for the larger veins running directly to the surface (*e.g* in the posterior column of the spinal cord, the veins dorsal to the olives, etc ) then easily finds an explanation The marginal gliosis is not especially localized in places with overlying large pial veins. We have also compared the frequency of affected veins in the more compact parts of the white matter with that in the more loosely built parts, but have not found a conclusive difference (although the corpus callosum, cerebral peduncles, optic tract and pyramids are generally little affected)

No definite solution can at present be given, but it may be remarked that the perivenous spaces in the brain are generally sites of predilection for oedema, and also for accumulation of fatty granule cells in processes of degeneration These cells may be found a long time after a malacic accident, still lying in exactly the same places where demyelination and microglial proliferation occur in perivenous encephalitis. Also, in chronic atrophy of the brain, we find widened perivenous spaces filled with clear fluid, with the same localization. Perhaps the structure around these veins is less dense than in other places and can be more easily distended This distension is also

necessary in hyperaemia, because the increased flow of blood in the arteries is due to the increased rate of flow, in the capillaries to a greater number of capillaries filled, but in the veins it must be due to greater distension of these vessels.

Continuing this line of thought, we might suggest that processes *which start with a toxic action on the vessel wall can primarily affect* all the vessels, larger and smaller ones, whereas processes starting with a disturbance of the perivascular fluids (in the Virchow-Robin space, or even in the parenchyma) would, by preference, take place around the medium-sized veins.

We could also suggest that the veins are the places of predilection, because high molecular substances cannot be absorbed by the capillaries, but have to be broken down to low molecular weight and that this is done in the Virchow-Robin space, which does not exist *around capillaries (Farquhar, 1957, and others). This might* be important when we consider this encephalitis to have an allergic basis (Boyd, 1947, antigens cannot pass the wall of the veins).

The subpial marginal glia could likewise aid in transporting substances directly to the arachnoidal spaces, after breaking them up into substances of lesser molecular weight.

The disturbance of the enzymic processes of this kind of glia would then cause degeneration of the myelin (Roizin; Huszak, 1958).

The *demyelination* is always focal and must therefore have its cause *locally. This could either be a chemical substance*, diffusing from the perivascular space into the parenchyma and acting directly on the myelin, or a substance or agent acting on the oligodendroglia. Microscopically, however, changes of the oligoglia, except slight hypertrophy, are not found in our preparations.

In our slides, demyelination and microglial proliferation occur together No foci of either one or the other can be found, but we already said that to our opinion the demyelination is not caused by microglial proliferation, but that both probably are the result of some noxious agent.

Scholz remarked, that microglial proliferation goes far beyond what is generally seen in small necrotic foci, and only part of this probably

must be regarded as a reaction to the myelin decomposition products.

*Myelin* is a rather labile chemical substance, reacting to a number of conditions by chemical changes of which swelling and lessened stainability by our usual techniques are most easily recognized. The oedema around a tumour (Greenfield) or in hypoxia (Scholz) may cause a serious change in our myelin-stained slides, although probably much of the substance is still present. The reaction of the surrounding glial tissue in these conditions varies with aetiology. Oedema round a tumour often does not cause microglial proliferation and only slight oligoglial hypertrophy. In a malacic focus, however, the microglia will react by the formation of fatty granule cells.

Well known is also the metachromatic myelin breakdown in some groups of leucodystrophy. Von Hirsch and Peiffer (1955) distinguish two main types of catabolic products, the sudanophile substances and the prelipids, and suggest specific changes in the various lipidoses. In this respect too, perivenous encephalitis therefore has a separate place in the histopathological pictures and it is not preposterous to suppose that this special picture must have a special biochemical cause, differing from what we know in other conditions.

The breakdown of myelin to a substance of low molecular weight is necessary because myelin, which is absorbed into the blood, gives rise to the formation of iso-antigens.

Although a discussion of the theory of an *allergic pathogenesis* of the perivenous encephalitis is outside the scope of this treatise, some words must be said about it, because the picture we consider the typical histopathology of microglia encephalitis differs in many points from allergic inflammation in other organs. Here, the reaction is primarily vascular, with proliferation of the wall, oedema and cellular perivascular infiltration by mononuclear or polynuclear cells, which is only the minor part in microglia encephalitis and may even be entirely absent. Also, the absence of eosinophils in the latter, is stressed by nearly all authors.

However, a number of other symptoms and signs point in the direction of an allergic reaction: the incubation time of 9—14 days; the very short period of outbreak of the symptoms, followed by

recovery or death; the therapeutic influence of ACTH; the affection of only a small part of the population; the great influence of differences in constitution (previous vaccination; influence of other diseases or injections; influence of stress, etc.); the focal character of the lesions; the monomorphous character of the uncomplicated cases; the fact that perivenous foci can be experimentally produced by methods generally causing allergic reactions, although these are combined with the usual vascular changes.

Even the fact that microglia encephalitis does not occur in young babies points in the same direction, when we bear in mind that experimental allergic encephalitis cannot be produced when brain from new born animals is used, in which normal myelin development has only started, and the brain of the very young child differs in myelin composition from the older brain.

This brings us to the supposition that some process, not the well-known allergy but something akin to it, in some way is responsible for the development of microglia encephalitis following exanthematous diseases.

*Chapter 7*

# CONCLUSIONS

1. The clinical disease postvaccinial encephalitis comprises several pathologically different diseases of the C.N.S., which often cannot be distinguished before an autopsy reveals their nature. Thus acute anterior poliomyelitis, occurring shortly after vaccination, has been repeatedly diagnosed as postvaccinial encephalitis until autopsy showed its true nature.

2. One of the clinico-pathological diseases following smallpox vaccination is called perivenous or microglia encephalitis It is characterized by the following facts. It occurs following smallpox ccination and a few other exanthematous diseases, and very rarely fter other diseases.

It has an incubation period of 9—15 days (with one possible exception of 28 days), runs an acute course and, when no complications occur, leaves no sequelae (except when myelitis is the main localization).

It has very rarely been noted before 1923, it does not occur in children under two years of age, and is absent in patients in whom revaccination results in immunity reaction of the skin

It has a very specific histological picture, differing from encephalitis caused by a living agent and from the usual reaction of the C N S to toxi-infectious conditions.

The name microglia encephalitis is used in this treatise for those cases in which histological examination verified the existence of this special type

3 Smallpox vaccination can also be followed by other nervous complications with clinical symptoms and pathological changes similar to those following other infectious diseases Of these, encepha-

lopathy and convulsions are frequent in young children; haemorrhagic encephalitis is sometimes seen in children and adults.

4. Smallpox vaccination may also influence (stimulate, activate?) the outbreak of other virus diseases (herpes encephalitis; poliomyelitis; epidemic encephalitis; myocarditis).

5. Microglia encephalitis occurs relatively more often after vaccinia than after measles, and rarely after rubella and varicella. It is extremely rare following other diseases or occurring without clear aetiology.

The occurrence in pox virus affections is inversely proportional to the seriousness of the disease: not observed after typical smallpox; sometimes found after alastrim or very mild smallpox and rather often after vaccinia.

6. The incubation period in microglia encephalitis following revaccination *is the same as when following primary vaccination. No clear* accelerated reaction can be found. But when revaccination is followed by another pathology, the incubation is showing a wide range of dispersion as is also seen when primary vaccination is followed by the toxi-infectious reaction types.

7. A fatal clinical course depends on the main localization of the process in the brainstem, pons and oblongata rather than on the number of foci and the incubation time. It is independent of the seriousness of the skin reaction to the vaccination.

8 When microglia encephalitis runs a fulminant course, the histopathological picture has already fully developed. We find no indication that a vasculo-encephalopathic reaction should have preceded this. Cases of fulminant death in which only changes of encephalopathy are found, should therefore not be considered very early or incipient cases of perivenous encephalitis.

9. The foci of perivenous microglial proliferation are always distributed along the entire nervous axis, but they may be more numerous in the hemisphere or the deep ganglia, or pons and oblongata, or in the spinal cord. Localization chiefly in pons and oblongata is probably the most dangerous to life.

The spinal cord is affected in all cases, but symptoms of transverse

myelitis are generally not conspicuous when the cerebral symptoms dominate the picture. Death in these myelitis cases often comes on after a longer illness than in the cerebral cases and is mostly due to complicating diseases (decubitus; purulent infections, pneumonia) When the patient survives, sequelae may be present for a certain period

10 Following smallpox vaccination, we can expect a certain number of patients to have subclinical signs of cerebral (or spinal involvement, which could perhaps be diagnosed by E.E.G and albumin or globulin changes in the C.S.F. This has been demonstrated in measles and parotitis, and E.E.G. changes after vaccination point in the same direction. We could regard these patients as sensitized in some way and therefore more vulnerable to exogenous factors, to which they might react with the development of an encephalitis.

11. The perivenous type of clinical postvaccinial encephalitis consists of slight diffuse pia infiltration by lymphocytes, marginal gliosis and focal demyelination and microglia cells, lying in the parenchyma around veins Small lymphocytes are found in nearly all cases in small numbers and, therefore, probably belong to the picture Other cell types, as polynuclears and erythrocytes, are not a part of microglia encephalitis. The presence of these blood cells probably always points to other factors (as bronchopneumonia, other serum injections, lowered resistance of the brain due to earlier disease or trauma) acting at the same time.

12. The myelin degeneration is not observed with our staining technique before glial hypertrophy is evident, but there is reason to believe that some degeneration of the myelin has taken place, the microglial proliferation being partly a reaction to this

The breakdown of the degeneration products of the myelin can obtain in the smaller foci by a chemical change into soluble substances, which are then transported to the circulation However, in the larger foci the amount of catabolic material is larger and a change into fat and fatty acids occurs, which can be found by Sudan stains

13 Marked oedema is not an outstanding characteristic of microglia encephalitis, although it was very evident in a few cases

It is on the contrary very much in evidence in cases of encephalopathy, whether following vaccination or toxi-infectious conditions.

14. When patients suffering from postvaccinial microglia encephalitis die from bronchopneumonia or from other complications, histological changes (haemorrhages, thromboses, tissue necrosis) may be found, which do not belong to the picture of the original disease.

15. The perivenous microglial foci are a special reaction type of the nervous system, which is the most important pathology in post-exanthematous microglia encephalitis but may be occasionally met in other conditions, of which poliomyelitis must be mentioned in the first place. But pictures highly resembling these foci can also be encountered in embolic and haemorrhagic encephalitis, following contusion of the brain, and other diseases.

16. A sharp division should be made between the perivenous microglial foci and the vascular toxi-infectious foci, which fall into a different class of reactions The border between microglia encephalitis and disseminated encephalomyelitis is less sharp, and cases occur in which histopathological examination does not allow a decision as to the group to which a case belongs.

17. Cases of encephalitis following revaccination are often not so monomorphous as those after primary vaccination. The clinical course and the pathology may show some differences, which are more marked when a low degree of immunity still exists.

18 The rôle played by the veins in the demyelinating process is still unknown; a suggestion is given that the width and function of the perivenous space might be more important than the circulation of the blood in these vessels.

19 Post-exanthematous microglia encephalitis is probably not directly caused by a virus or other living agent but is due to more complicated interaction of high-molecular substances, formed by conditions which in some points resemble allergic processes.

20 Because the name perivenous or microglia encephalitis, comprises more than is originally meant, it is proposed to introduce the name disease of Turnbull, Lucksch, Bastiaanse, for the special type circumscribed here.

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# INDEX

# CLINICAL AND PATHOLOGICAL REMARKS

Pertussis infection when vaccinated. Had 4 inj. against this. Haemorrhages from hyperaemic vessels. A few *ring haemorrhages. Bacteria in vessels (autopsy* 39 h post mortem). 10th day convulsion

Pia 50% polynuclears, thick infiltrate. Marked cortical cell loss and oedema in *4th to 6th layers*

Pyramidal cells still in subcortical white matter

Many rod cells in cortex, diffusely. Sudan fat along vessels

Small foci, but very dense. Glial stars. Marginal gliosis as thick microglial masses. Degeneration of subst. nigra. C.S.F. many cells

Very compact foci

Old lipochrome pigment along vessels in cortex. Atrophy around post. horn of ventr. Mostly fresh haemorrhages round several vessels. In thor. cord some glial stars

Many foci in cortex, small and large, perivasc. Marked large-cell meningitis.

Foci compact, rather small and well defined

Foci rarified, distributed far in the tissues. Many microglial granule cells. Abnormal mitotic divisions

Temp. down to normal, then bronchopneumonia. Foci centrally dense, rod *cells very diffuse in cortex. Upper layers free*

Foci rarified, far in tissues

: ... before death coma (serum inject ?)

Thypus-cholera inj. at time of vacc. and twice later. Old blood pigment in vessel sheaths

Convulsion 11th day. Cystitis. Normal temp. last 5 days, except day of death. Foci of different age.

12th day cerebral symptoms. 15th day transverse *myelitis complete*. Chromatolysis of ant. horn cells in spinal cord. Here also typical lesions.

Fresh erythrocytes in Virchow-Robin space in pons, oblongata in foci or without microglia. Chromatolysis of ant. horn cells in spinal cord

Swelling of brain. Foci of haemorrhagic encephalitis separate from the micro-*glial foci*

Status dysraphicus

Cystitis purulenta. Starting purulent meningitis? Ganglion cell necrosis in spinal cord